IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Application of	:	
Leslie BAUMANN *et al.*	:	Group Art Unit 1623
Serial No. 10/627,994	:	Examiner Olson
Filed: July 28, 2003	:	
For: Method for Treating Damaged Skin	:	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Supplemental 1.131 Declaration of Leslie S. Baumann, M.D.

I, Leslie S. Baumann, being duly sworn, depose and say:

1. I am the co-inventor of US Patent Application Serial No. 10/627,994 and submit this declaration pursuant to 37 C.F.R. § 1.131 for further consideration by the US Patent and Trademark Office in connection with this application.

2. Dr. Welsh and I conceived the claimed invention – the cosmetic use of Aldara for the treatment of fine lines and clinical wrinkles on normal, photo-damaged skin – prior to March 13, 2003. Conception was followed by diligence until reduction to practice, which was accomplished both through the treatment of patients and through the filing of US Patent Application Serial No. 10/627,994.

3. Our conception of the claimed invention is reflected in the Invention Disclosure that we filed on June 20, 2002 with the Office of Technology Transfer at the University of Miami. In that disclosure, we reported our observation that "when imiquimod cream ... is used for an off FDA label use, the skin looks healthier and there are fewer clinical wrinkles." In describing this use as an "off FDA label use," we were referring to the fact that Aldara is a prescription medication that was approved by the FDA in March 1997 for

the treatment of external genital and perianal warts. (A copy of the Invention Disclosure is attached as Exhibit A.)

4. In this Invention Disclosure, we indicated that conception of the claimed invention occurred in December 2001 – specifically, in discussions between Dr. Welsh and me at the University of Miami Department of Dermatology Cosmetic Center.

5. Our idea that Aldara could be used for a cosmetic purpose (*i.e.*, reducing the appearance of fine lines and clinical wrinkles in normal, photo-damaged skin) is further reflected in the clinical trial protocol I wrote with Dr. Welsh that was submitted to, and approved by, the University of Miami's Institutional Review Board ("IRB"). The process by which this protocol was created and approved is described below.

6. From January 2002 to the start of the IRB-approved clinical trial, 3M sales representatives visited our medical practice at the Cosmetic Center once per month (on average). On each visit, 3M sales representatives would provide our office staff with four to seven packets of Aldara (on average). A July 8, 2004 memorandum from Laura Black, MA, MPH (a Senior Research Associate at the Cosmetic Center) reflects that packets of the Aldara study medication were obtained from 3M sales representatives. Specifically, the memorandum indicates that 108 packets of the "office samples from pharmaceutical reps." had been obtained on various dates prior to September 2003. (A copy of this memorandum is attached as Exhibit B.)

7. Because our clinical study on the use of Aldara to treat normal, photo-damaged skin for fine lines and clinical wrinkles involved the daily application of Aldara, we needed to obtain a sufficient supply of the medication. Recognizing that amassing the necessary supply through samples by 3M sales representatives would be an impracticably lengthy process, we contacted 3M in the hope of obtaining a larger sample supply. Since 3M did not agree to provide the larger supply, our medical practice

purchased additional Aldara from Cedars Medical Center Pharmacy to be used as clinical practice sample supplies. This is discussed in Paragraph 14 below.

8. Prior to and following the submission of our Invention Disclosure, I treated patients at the University of Miami Cosmetic Center for photoaging with Aldara. While we were procuring sufficient samples of Aldara for the purpose of conducting our clinical study, I continued to treat patients for photoaging with Aldara. A page from a patient chart with an entry dated September 10, 2002 is attached as Exhibit C. This entry describes my treatment of a patient at the University of Miami Cosmetic Center for photoaging by nightly administration of Aldara. (The identity of the patient has been redacted for reasons of protecting patient privacy.) The chart note reads: "9/10/02 - Aldara Qhs to face prn photoaging." "Qhs" is the acronym for the Latin phrase *quaque hora somni* (every hour of sleep). Physicians use this acronym in their chart notes (and on prescriptions) to direct administration of a treatment every night.

9. On November 4, 2002, Dr. Welsh created a document with the following title:

PROTOCOL
TITLE: Pilot Study of the Use of Aldara for the Treatment of Photoaging
Principal Investigator: Leslie S. Baumann, M.D.
Co-Principal Investigator: Esperanza Welsh, M.D.

This was the first draft of the study protocol that was submitted to, and ultimately approved by, the University of Miami's IRB. This draft further reflects our earlier observations that Aldara could be used for the treatment of photo-damaged skin – specifically reducing fine lines and clinical wrinkles.

10. On November 12, 2002, Joy M. Bryde, MSW, sent Dr. Welsh comments on the draft document described in Paragraph 9 above. At this time, Ms. Byrde was the director of clinical research at the Cosmetic Center.

11. Through the end of November and continuing to mid-December 2002, Dr. Welsh reviewed and revised the draft study protocol based on Ms. Bryde's comments. During this period, Dr. Welsh also completed an IRB training course required by the University in order to be listed as an investigator. On December 16, 2002, Dr. Welsh e-mailed a revised draft to Ms. Bryde for her further review and comment. (The e-mail exchange between Dr. Welsh and Ms. Bryde is attached as Exhibit D. In addition, a copy of the December 16, 2002 version of the draft protocol is attached as Exhibit E.)

12. From January 2003 though June 2003, I, together with Dr. Welsh, worked on finalizing the protocol for the pilot study of treating photo-damaged skin with Aldara. During this period, we developed all of the case report forms to be completed by investigators, patients, and independent dermatologists (who would complete blinded assessments of a series of photographs taken of each participant over the course of the study). In addition, during this same period, we developed participant instructions, informed consent forms, and advertisements for patient recruitment. These forms were submitted to University attorneys for their review and approval prior to the submission of the protocol to the IRB. (This process required several revisions and resubmissions to the University attorneys before our IRB submission was made). The advertisements were then reviewed by the IRB and revised. (A copy of the approved IRB Protocol is attached as Exhibit F.)

13. As part of an academic institution, the Department of Dermatology Cosmetic Center operates under significant financial constraints. Up until the Aldara study, the clinical trials conducted at the Cosmetic Center were industry-sponsored or done under a government grant. Further, because of the Cosmetic Center's budget limitations in 2001 and 2002, we did not have certain clinical assessment instruments needed for photoaging studies. Two such instruments – Visioscan® which measures the texture of

facial skin and Tewameter® which measures water loss from facial skin) – were purchased for the pilot study and our staff was trained on their use.

14. Since the Aldara pilot study was self-funded by the Cosmetic Center, during the first six months of 2003, we had to raise funds not only to cover the costs of additional Aldara (above that provided by 3M sales representatives), clinical assessment instruments, and clinical photography but also to make the requisite IRB payments.

15. On May 12, 2003, the University of Miami released rights to the invention of using Aldara for the treatment of photo-damaged skin, as now claimed in the US Patent Application Serial No. 10/627,994. Upon receiving this release, I interviewed and engaged patent counsel and caused the instant application to be filed. (A copy of the release is attached as Exhibit G.)

The foregoing statements are made of my own knowledge and are true. I have been warned that willful false statements and the like are punishable by fine or imprisonment, or both, and that such statements may jeopardize the validity of the application or any patent issuing thereon.

Further Declarant says not.

Dated: August 8, 2008

Leslie S. Baumann, M.D.

Sworn to and subscribed before
me on this 8 day of August 2008.

NIDIA THWAITES
MY COMMISSION # DD 787021
EXPIRES: July 12, 2012
Bonded Thru Notary Public Underwriters

EXHIBIT A

UNIVERSITY OF Miami

CONFIDENTIAL

INVENTION DISCLOSURE

Office use only
Case Number UM03-06

Section 1: GENERAL INFORMATION

1. TITLE OF INVENTION (not exceeding 100 typed characters):

Use of Aldara® for the Treatment of Photoaged Skin

2. Please list the names, primary Department affiliation and contact addresses of all inventors filing invention disclosure. (An INVENTOR or CO-INVENTOR is an individual who has conceived or made Intellectual Contribution to develop essential elements of the invention(s).

INVENTOR(S)	POSITION	DEPARTMENT	ADDRESS	TELEPHONE	FAX
Bauman, Leslie	Associate Professor	Dermatology	1295 NW 14th St. South Building Suite K Miami FL 33125	305-324-7546	

3. Please provide information on grant support used for developing the invention. (An accurate and complete sponsorship information is necessary to fulfill University of Miami's obligations under research grants and contracts and Federal regulations.)

CONTRACT/GRANT NUMBERS	SPONSOR(S)	UM ACCOUNT #	PRINCIPAL INVESTIGATOR
Grant Number	Sponsor	Account Number	Last, First MI
None			

4. In the absence of extramural grant support, were University of Miami facilities used for developing the invention?

☐ Yes ☑ No. If yes. Please provide details:

5. Filing a patent application, under US Patent Laws, require following information on *conception*, and *reduction to practice* and *public disclosure* of the invention. (A brief description of the terms and their significance is provided in the instructions to complete this invention disclosure.)

Conception and Public Disclosure of information related to this invention	**Date**	**References/Comments** (Please indicate, Place, Date, Names of individuals, journals/periodicals or forum of presentation. Use separate sheet if necessary)
a. Date and place of *conception* of the invention. (Please indicate if this has been documented.)		Discussion in December 2001, at the Cosmetic Center at the Department of Dermatology
b. *First publication* containing description to enable a person, skilled in the field, to understand and make use of the invention (include theses, and date of submission and publication.)		None
c. *First public oral disclosure* of invention sufficient to enable a person, skilled in the field, to understand and make use of the invention		None at present; planning to conduct clinical trial
d. If the invention is unpublished and undisclosed, provide the *anticipated publication*, oral and electronic disclosure		None

date and any submissions made for potential publication.		

6. Has the invention been reduced to practice? ☐ Yes ☑ No.

If yes, please give the Date of first reduction to practice.

7. List any agreements that have been signed regarding this invention such as material transfer agreement(s) clinical trial, consulting contract, drug studies, acceptance of material from collaborators, etc.

None

Section 2: SCIENTIFIC AND TECHNICAL INFORMATION

1. **COMPLETE DESCRIPTION OF INVENTION:** (Describe the invention in sufficient details, not exceeding 4900 typed characters, such that the description should enable a person, ordinarily skilled in the field, to understand and reproduce the invention. The information provided essential to complete thorough patent and literature searches, and patentability analysis(es) by Office of Technology Transfer staff and/or Patent Attorneys. Since patent attorney fees are very high, complete information is highly desired.)

It has been observed that when imiquimod cream, whose primary indication is to treat basal cell carcinomas or actinic keratosis, is used for an off label FDA use, the skin looks healthier and there are fewer clinical wrinkles. The cream was applied on the patients 4 times daily. The patients stated they like the cream and that they would want to use it all over the face. Therefore it is our belief that this cream could be used for a cosmetic purpose, an additional indication.

This conclusion is pure observation on a few patients. A clinical trial is needed to be done as soon as possible to study if imiquimod, which stimulates the production of cytokines like interferon, has any effect on photoaging which has already occurred or on prevention of future photoaging. How it would work is unknown, and if it works is also unknown. Clinical trials and further studies are needed.

2. **Kindly attach all necessary illustrations used in describing the invention.** (If unpublished manuscripts or published articles are enclosed, please refer to the illustrations in the articles. Please include all nucleotide and deduced polypeptide sequences, chemical structures and machine designs that describe the invention.)

3. **LABORATORY RECORDS:** (Please indicate the physical location and reference numbers of applicable laboratory records, but do not enclose records.

None yet

4. **PRACTICAL FEATURES OF INVENTION** (Please provide information on the Practical features of the invention, such as what problem would it, or products incorporating the technology, solve and who would use it?):

It would be a treatment for photoaging (wrinkles).

5. **In what ways is the invention different from present technology now in use or being developed?** (Please also list all KNOWN COMPETITORS or ALTERNATE TECHNOLOGIES now available or being developed.)

Currently it is FDA approved for the treatment of genital warts, and it is being studied for the treatment of skin cancer.

6. **List and briefly describe the products, services or commercial process that may result from and/or incorporate the invention as a technology component.** (Please envision all possible products, services or commercial processes and enlist them with brief details.)

Moisturizing creams with the active ingredient to prevent or treat photoaging.

7. **If further research and development is necessary or desirable before showing the invention to potential licensee, please estimate the following: Length of time: 1 – 2 years; Cost:** unknown

8. **bPlease list the major questions that must be addressed for completing the research work:**

1. Does it really work or is it only a few coincidental cases?

2. If it works, how often should it be applied and for how long must it be applied before change is apparent?

8. **Are there any ways to get around your invention?** (Please provide a brief account of other potential competing ways of developing your invention. The information would be necessary for obtaining an effective patent protection on the invention.)

No

9. **Please list related patents and research articles referenced in your response to other questions in section 2.**

A search was completed. Nothing was found which related imiquimod and any of the following categories: photoaging, wrinkles, elastosis or skin damage.

Section 3: MARKET INFORMATION

1. **What is the ideal market for this invention/technology?** (Please provide information on the composition of the ideal market, *if available*, whose needs this invention addresses. Please also provide information on various segments of the market.)

Male or female patients interested in photoaging treatment and/or prevention.

2. **Based on the function(s) of your invention, tell us something about why this is a useful invention in the marketplace and for the end users?** (Your response is optional.)

Everyone is in the search of the fountain of youth. Could this be a treatment for photoaging?

3. **What is the estimated size of the market in annual dollars?** (Your response is optional.)

☐ **less than $10,000** ☐ **$10 - 100,000** ☐ **$100,000 - $1 million** ☑ **over $1 million**

How did you derive this figure? (Please provide supporting data.)

Many cosmetic companies have topical products which treat photoaging with varying degrees of effectiveness. As new items enter the market, I have seen these prospective market figures estimated even higher. The aging baby boomer population is a significant size of consumers for this type of product.

4. **What factors, if known, influence the demand for this invention in the marketplace?** (Your response is optional)

Youth and beauty is constantly searched by many people.

5. **Please list the companies that may be interested in licensing the invention. Please also include the names of the experts that you may have dealt with in the past at the companies that may be interested in licensing the technology.**

3M owns Aldara® now but I do not believe they have any patented its use for photoaging.

6. **If you are aware of a definitive commercial licensee or a research sponsor who will license this invention, you must share details with OTT. Please indicate the company, contact person, address and telephone number.**

Company	Address	Contact	Telephone/Fax

Section 4: SIGNATURES (All Inventors must sign)

Name, title, signature and percent contribution of each person who made an INTELLECTUAL CONTRIBUTION to the invention described in this disclosure. According to the Patent and Copyright policy of the University of Miami the proceeds received by the University, after costs are recovered, will be distributed among the inventor(s), and other entities within the University. Respective intellectual contributions of the co-inventors outside the University of Miami should also be mentioned with their primary department and institutional affiliation. Co-inventors who are not University of Miami employees must complete section 6, page 7, to provide their residential addresses and social security numbers; the information is used later if patent applications are filed. (Use Section 5, page 7, or additional sheets of paper, if necessary.)

I (we) hereby declare that all statements made in this invention disclosure are true and accurate to the best of my (our) knowledge.

Inventor's Signature _____ Date 6/17/02

Leslie S. Baumann, MD
Name

50%
Interest

Dermatology, School of Medicine
Department

Inventor's Signature _____ Date 6/12/2

Esperanza Welsh, MD
Name

50%
Interest

Dermatology
Department

Inventor's Signature _____ Date _____

Name xxx%
Interest

Department

Inventor's Signature _____ Date _____

Name xxx%
Interest

Department

Inventor's Signature _____ Date _____

Name xxx%
Interest

Department

Inventor's Signature _____ Date _____

Name xxx%
Interest

Department

Signatures of two witnesses are required who understand the technical aspects of the invention

Technology disclosed to and understood by:

Name [signature]	Name FRANCISCO KENDEL MD
Signature [signature] Date 5/23/02	Signature [signature] Date 5/24/02

Section 5: ASSIGNMENT (All University of Miami Inventor(s) Must Sign)

Consistent with my (our) obligations set out in the University of Miami Patent and Copyright Policy, in the University of Miami Faculty Manual, the Policies and Procedures Manual, the Graduate Studies Bulletin, and the Undergraduate Studies Bulletin, I hereby execute this Assignment and "other documents as may be required" to comply with the provisions of the publications mentioned above. Additional assignment documentation may be required at the time of patenting. I (we) also agree to cooperate with the University of Miami Office of Technology Transfer in the protection and commercialization of this invention.

In consideration of One dollar ($1.00) and other good and valuable consideration paid to me by the UNIVERSITY OF MIAMI, a Not-for-Profit Florida Corporation, the receipt and sufficiency of which are hereby acknowledged, I hereby sell, assign and convey to the UNIVERSITY OF MIAMI, its successors and assign, the full and exclusive right, the title and interest in and to this invention as described in this invention disclosure and to the patents that may issue theron for the full benefit and behoof of said UNIVERSITY OF MIAMI.

Inventor's Signature [signature] Date 5/22/02 Leslie S. Baumann, MD Name Home Address USA Social Security Number / Country of Citizenship	Inventor's Signature [signature] Date 6/12/2 Name Home Address XXX-XX-XXXX Country Social Security Number / Country of Citizenship
Inventor's Signature Date FirstName MiddleName LastName Name Street address, City, State, ZIP Home Address XXX-XX-XXXX Country Social Security Number / Country of Citizenship	Inventor's Signature Date FirstName MiddleName LastName Name Street address, City, State, ZIP Home Address XXX-XX-XXXX Country Social Security Number / Country of Citizenship
Inventor's Signature Date FirstName MiddleName LastName Name Street address, City, State, ZIP Home Address XXX-XX-XXXX Country Social Security Number / Country of Citizenship	Inventor's Signature Date FirstName MiddleName LastName Name Street address, City, State, ZIP Home Address XXX-XX-XXXX Country Social Security Number / Country of Citizenship

STATE OF FLORIDA
COUNTY OF MIAMI-DADE

The foregoing instrument was acknowledged before me this 30 day of Oct 2002, by above, who is personally known to me or has produced DMFI as identification and who did take an oath.

NOTARY PUBLIC

Signature N. Coelho

Printed Name Nicole Coelho

State of Florida at Large

Nicole Coelho
My Commission DD039340
Expires July 04, 2005

My commission expires:

Section 6: ADDRESSES OF CO-INVENTORS EMPLOYED BY OTHER INSTITUTIONS

Esperanza Welsh, MD Name Home Address US Social Security Number — Country of Citizenship MEXICO	FirstName Last Name Name Street address, City, State, ZIP Home Address SSN Country US Social Security Number Country of Citizenship
FirstName Last Name Name Street address, City, State, ZIP Home Address SSN Country US Social Security Number Country of Citizenship	FirstName Last Name Name Street address, City, State, ZIP Home Address SSN Country US Social Security Number Country of Citizenship
FirstName Last Name Name Street address, City, State, ZIP Home Address SSN Country US Social Security Number Country of Citizenship	FirstName Last Name Name Street address, City, State, ZIP Home Address SSN Country US Social Security Number Country of Citizenship

Completed Invention Disclosure should be marked CONFIDNETIAL and hand-delivered or sent by inter-office mail to the Director, Office of Technology Transfer, University of Miami, Dominion Tower, Suite 906 (M-811). Telephone 243 5689, Facsimile: 243 3510.

Section 5: ASSIGNMENT (All University of Miami Inventor(s) Must Sign)

Consistent with my (our) obligations set out in the University of Miami Patent and Copyright Policy, in the University of Miami Faculty Manual, the Policies and Procedures Manual, the Graduate Studies Bulletin, and the Undergraduate Studies Bulletin, I hereby execute this Assignment and "other documents as may be required" to comply with the provisions of the publications mentioned above. Additional assignment documentation may be required at the time of patenting. I (we) also agree to cooperate with the University of Miami Office of Technology Transfer in the protection and commercialization of this invention.

In consideration of One dollar ($1.00) and other good and valuable consideration paid to me by the UNIVERSITY OF MIAMI, a Not-for-Profit Florida Corporation, the receipt and sufficiency of which are hereby acknowledged, I hereby sell, assign and convey to the UNIVERSITY OF MIAMI, its successors and assign, the full and exclusive right, the title and interest in and to this invention as described in this invention disclosure and to the patents that may issue theron for the full benefit and behoof of said UNIVERSITY OF MIAMI.

Inventor's Signature Date 10/30/02	Inventor's Signature Date 10/30/2
Name Leslie Baumann	FirstName MiddleName LastName Name Esperanza C. Welsh
Home Address	Street address, City, State, ZIP Home Address
Social Security Number Country of Citizenship USA	XXX-XX-XXXX Country Social Security Number Country of Citizenship
Inventor's Signature Date	Inventor's Signature Date
Name	FirstName MiddleName LastName Name
Home Address	Street address, City, State, ZIP Home Address
Social Security Number Country of Citizenship	XXX-XX-XXXX Country Social Security Number Country of Citizenship
Inventor's Signature Date	Inventor's Signature Date
FirstName MiddleName LastName Name	FirstName MiddleName LastName Name
Street address, City, State, ZIP Home Address	Street address, City, State, ZIP Home Address
XXX-XX-XXXX Country Social Security Number Country of Citizenship	XXX-XX-XXXX Country Social Security Number Country of Citizenship

EXHIBIT B

UNIVERSITY OF Miami
SCHOOL OF MEDICINE

Memorandum

To: Investigator Trial File

From: Laura Black, MA, MPH LJB
Senior Research Associate

Date: 8 July 2004

Protocol Number: 2003-0507C

Title: "Pilot Study of the Use of Aldara™ (imiquimod 5%) for the Treatment of Photoaging"

Re: **Reconciliation of Study Medication**

This memorandum is to document the reconciliation of the study medication for the above named study. A total of 348 packets of study medication were available for this study; 320 were used by participants. The packets of medication came from the following sources:

Date	Source	Number of Packets
Unknown—various dates	Office samples from pharmaceutical reps.	108
9/15/03	Office samples from pharmaceutical rep.	24
10/21/03	Cedars Medical Center Pharmacy	60
11/10/03	Cedars Medical Center Pharmacy	96
12/10/03	Cedars Medical Center Pharmacy	60
	Total:	348

Unused packets of study medication (n=28) have been returned to the clinical practice sample supplies.

Cedars Medical Center
1295 N.W. 14th Street
South Building, Suite K
Miami, Florida 33125

UM Cosmetic Center
Division of Cosmetic Dermatology
Department of Dermatology
and Cutaneous Surgery

305-324-SKIN (7546)
305-324-HAIR (4247)
Fax: 305-324-9249
http://derm.net

EXHIBIT C

UNIVERSITY OF MIAMI COSMETIC CENTER

Physician's Progress Notes

4/23/02 TCA peel today 30% to scalp areas p 1 coat of Miami Peel

[signature]

5/28/02 Not using Tazorac x 2-3 weeks.

Will enroll in Pan Retin trial.

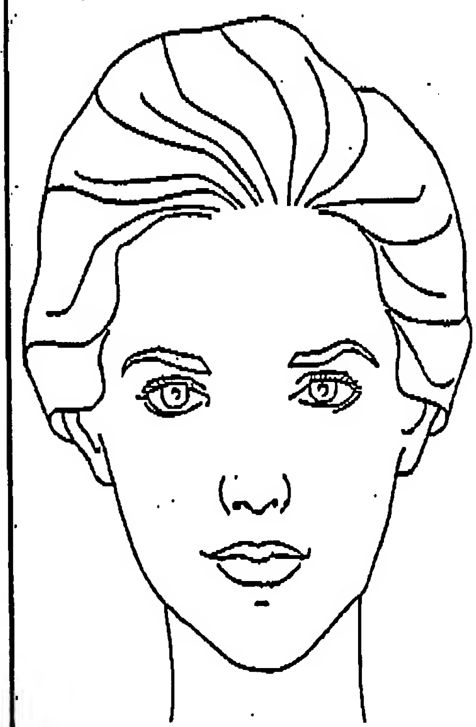
[signature] MD

6/11/02 Enroll Pan Retin trial

[signature]

9/10/02 Aldara Qhs to face prn photos as [illegible]

photos taken week 16 Pan Retin al.



Patient Identification

[redacted]

EXHIBIT D

Black, Laura

From: Esperanza Welsh [esperanzaw@hotmail.com]
Sent: Monday, December 09, 2002 1:24 AM
To: jbryde@derm.net
Subject: Re: FW: Aldara forms

Thnkyou, my Thanksgiving was very good! Regarding the baby, its going well too. Regarding the protocol, I am almost done with the changes. I'll email it to you soon.

Espe

>From: "Joy M. Bryde"
>Reply-To:
>To: ""Esperanza Welsh""
>Subject: FW: Aldara forms
>Date: Fri, 6 Dec 2002 16:41:52 -0500
>
>Hi Esperanza-
>
>Hope you had a good Thanksgiving and the pregnancy is going well.
>I was just reviewing pending items and came across this protocol. Do
u have any questions or need any feedback?
>
>let me know!
>
>Joy
>
>
>
>
>-----Original Message-----
>From: Joy M. Bryde [mailto:jbryde@derm.net]
>Sent: Tuesday, November 12, 2002 4:41 PM
>To: 'Esperanza Welsh (esperanzaw@hotmail.com)'
>Cc: 'Leslie Baumann M.D.'
>Subject: Aldara forms
>
>
>Hi Esperanza-
>
>I've taken a look at the protocol, informed consent and participant
>instructions. They look really good! This is great little study and I
>know Dr. B is really excited about it.
>
e put in some comments and inserts into sections where it needed to
>be clarified or expanded through the tracked changes tool in Word so
>you'll be able to see the comments easily. Some of the changes are
>simply due to our increased knowledge of what the IRB likes to see.
>Overall as a reminder, the Informed consent truly has to be in 6th grade

>language. such things as photoaged skin have to be defined....sigh.
>I'm not sure about how to explain genital warts yet!
>
>Also, as you see, I resaved with my initials so you know they are the
>sion I worked on. Go ahead and resave under your initials with the
>date you work on them.
>If you have any questions, let me know!
>
>Joy
>
>PS As a reminder, we can't list you as as an investigator or even key
>personnel until you've completed the IRB course!
>
>
>
>
>
>
><< AldaraStudySkinCareInstructions12NOV02jmb.doc >>
><< AldaraIC12Nov02jmb.doc >>
><< FINALProtocol12nov02jmb.doc >>

Black, Laura

From: Esperanza Welsh [esperanzaw@hotmail.com]
Sent: Monday, December 16, 2002 1:45 AM
To: jbryde@derm.net
Subject: Re: Aldara forms
Attachments: AldaraStudySkinCareInstructions12NOV02jmb (REV EW).doc; FINALProtocol12nov02jmb (REV EW).doc

Joy:

Here are two of the corrected files ready. I did a lot of changes. I had trouble with one of the files you sent me. I lost it and have to redo it again. Eduardo told me that probably it has a virus or it has too many corrections. I'll do it again in the afternoon tomorrow and will send it to you. I did the IRB thing already and I am waiting for the diploma. Attatched are my 2 revised files.

Take care,

Espe

>From: "Joy M. Bryde"
>Reply-To:
>To: "'Esperanza Welsh'"
>CC: "'Leslie Baumann M.D.'"
>Subject: Aldara forms
>Date: Tue, 12 Nov 2002 16:40:41 -0500
>
>Hi Esperanza-
>
>I've taken a look at the protocol, informed consent and participant
>instructions. They look really good! This is great little study and I
>know Dr. B is really excited about it.
>
>I've put in some comments and inserts into sections where it needed to
>be clarified or expanded through the tracked changes tool in Word so
>you'll be able to see the comments easily. Some of the changes are
>simply due to our increased knowledge of what the IRB likes to see.
>Overall as a reminder, the Informed consent truly has to be in 6th grade
>language. such things as photoaged skin have to be defined....sigh.
>I'm not sure about how to explain genital warts yet!
>
>Also, as you see, I resaved with my initials so you know they are the
>version I worked on. Go ahead and resave under your initials with the
>date you work on them.
>If you have any questions, let me know!
>
>Joy
>

>PS As a reminder, we can't list you as as an investigator or even key
>personnel until you've completed the IRB course!
>
>
>
>
>
><< AldaraStudySkinCareInstructions12NOV02jmb.doc >>
><< AldaraIC12Nov02jmb.doc >>
><< FINALProtocol12nov02jmb.doc >>

EXHIBIT E

UM COSMETIC CENTER

Aldara Clinical Research Study Skin Care Instructions

Morning:

1. Wash face with Cetaphil Cleanser
2. Apply Cetaphil Moisturizer
3. Apply Vanicream Sunscreen
4. Apply makeup as usual

Evening:

1. Wash face with Cetaphil Cleanser

Apply a pea size of Aldara to face dividing it evenly on the face. The aldara cream will be used every other night as directed.Apply Cetaphil Moisturizer over Aldara if desired.

4. If there is any irritation stop using the aldara for a day and apply cetaphil moisturizer, reapply aldara afterwards as directed. If there is no irritation continue using the aldara cream as well as the cetaphil moisturizer daily, if there is irritation stop the cream and notify the research group.

Formatted: Bullets and Numbering

Deleted: ¶
¶

PROTOCOL

TITLE: Pilot study of the use of Aldara™ for the treatment of Photoaging

Principal Investigator: Leslie S. Baumann, M.D.
Co-Principal Investigator: Esperanza Welsh, M.D.

1.0 BACKGROUND INFORMATION:

Aldara is an FDA approved topical therapy for the treatment of genital warts. Imiquimod topical 5% induces the production of several cytokines such as interferon which is known to aid in the elimination of viral infections such as the one caused by genital warts. These cytokines might also have an effect on photoaging.

It has been shown in case series that Aldara cream also plays a role in the elimination of skin cancers such as basal cell carcinomas through the induction of cytokines. While the anticarcinogenic effects are beyond the scope of this pilot study, it is important to determine whether this compound can be used in these particular areas without major side effects.

2.0 TRIAL OBJECTIVE:

The primary objective of this study is to evaluate the safety and efficacy of Aldara cream in photodamaged skin.

3.0 STUDY DESIGN:

This study is an open label, pilot study for the use of Aldara cream for photoaging. It will involve 20 participants. Two weeks prior the commencement of the study will be assessed both clinically and demographically. At this time a clinical history will be done. The patient will be instructed to stop using any topical creams on the face, and a pregnancy test will be done.

At Day 0 the patients will get color and ultraviolet face pictures, get a visual analog questionnaire,

4.0 PRIMARY EFFICACY VARIABLES:

- Serial color and ultraviolet photography of study participant's face
- Physician assessments of face (through what mechanism)
- study participant assessments of face (through what mechanism)

5.0 PARTICIPANTS:

20 healthy volunteers

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Deleted: This will be an open label, pilot study of Aldara cream. Twenty participants with signs of photo-aging will be entered into the study. How is photoaging going to be determined? The study participants will be asked to discontinue the use of all topical medications to the treatment sites for two weeks prior to the study (This visit is 'the washout' and needs to be Day -2 weeks see section 10.0). On Day 0, the study participants will be provided with 12 packets of Aldara cream. Women of child-bearing potential will undergo a urine pregnancy test prior to receiving the study medication. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study. ¶
. Study participants will be asked to apply the Aldara to the face daily, and will be followed for a period of 16 weeks. Study participants will be provided with a mild soap and sunscreen to be used daily on treatment areas. In addition, study participants will be provided with a mild class V topical corticosteroid to apply to any redness, scaling, or itching which may develop at the study medication treatment sites. (Aren't these AEs? If we supply treatment in advance and have no tracking, then not noting full effects of cream)¶
. The study participant treatment sites will be evaluated on Day 0, Week 2, Week 4, Week 8, and Week 16 (what's the reason for this pattern?). At each visit, the study participant and Investigator will assess the appearance of XXXXX the following scale should be given a name and put in Appendix as #1) a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) telangectasias, and e) scaling. Each of these parameters will be graded on a 0-3 scale, 0= none, 1= mild, 2=moderate, 3=severe. Participants will also be evaluated for the presence of other photo-aged related lesions, such as actinic keratoses through what method and criteria?. ¶
At each visit the study participants will have color and ultraviolet photographs taken of their face. The Canfield photography system will be utilized to maintain consistency. After Week ... [1]

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6.0 INCLUSION/EXCLUSION CRITERIA:

6.1 INCLUSION CRITERIA:

- Age 18 years or older
- Healthy volunteers
- Informed consent given and signed by the participant
- Participant willing to follow instruction and return for follow-up visits
- Presence photo-damaged skin on face and hands (determined by what criteria?
- Negative urinary pregnancy test immediately prior to injection (?) for female study participants of childbearing potential
- Willing to discontinue the use of all topical medications to the treatment sites for two weeks prior to commencement of using study cream

6.2 EXCLUSION CRITERIA:

- Participation in another clinical research study and receiving treatment within the immediate previous 30 days
- Known allergy to study medication
- Unable to return for follow-up visits
- Female study participants who are pregnant, breastfeeding or planning a pregnancy during the course of the study

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7.0 MATERIALS AND METHODS:

7.1 Study Medications:

• All study participants will be provided with 12 packets of Aldara Cream. A small amount (about the size of a pea) will be placed on the palm of the hand and evenly distributed on face and dorsal hands.

• Study participants will be provided with a mild soap and sunscreen to be used daily on treatment areas.

7.2 Study Methods

This will be an open label, pilot study of Aldara cream. Twenty participants with signs of photo-aging will be entered into the study. Photoaging will include the appearance of fine and course wrinkles. The study participants will be asked to discontinue the use of all topical medications to the treatment site for two weeks prior to the study (This visit is 'the washout' and needs to be Day -2 weeks see section 10.0). On Day 0, the study participants will be provided with 12 packets of Aldara cream. Women of child-bearing potential will undergo a urine pregnancy test prior to receiving the study medication. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study.

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Study participants will be asked to apply the Aldara to the face daily, and will be followed for a period of 16 weeks. Study participants will be provided with a mild soap and sunscreen to be used daily on treatment areas. In addition, study participants will be instructed how to use the cream if there is aby irritation and to stop and notify us if this continues for more than a day. A class V topical steroid will be prescribed if necessary.

The study participant treatment site will be evaluated on Day 0, Week 2, Week 4, Week 8, Week 12, and Week 16. With this pattern of evaluation we will be able to see any adverse effects soon in the study, and we will be able to have a monthly evaluation. Also, the beneficial effects need to be evaluated at least 4 months after starting the cream. At each visit, the study participant and Investigator will assess the photoaging scale which will the overall improvement in a) fine wrinkles, b) coarse wrinkles and c) tactile roughness. Each of these parameters will be graded on a 0-3 scale, 0= none, 1= mild, 2=moderate, 3=severe. Participants will also be clinically evaluated for the presence of other photo-aged related lesions, such as actinic keratoses. The number of lesions will be counted.

At each visit the study participants will have color and ultraviolet photographs taken of their face. The Canfield photography system will be utilized to maintain consistency. After Week 16, the photographs will be evaluated by a blinded independent dermatologist, comparing the study participants' photographs with their baseline photographs to assess the efficacy of the study medication on photo-aging. The independent observer will use a photo-aging scale (as above, scale given a name and put in Appendix as #2, using 0=none, 1=mild, 2=moderate, 3=severe.

At Day 0 and Week 16, study participants will complete a visual analog scale (VAS) (add to appendix) to assess the cosmetic appearance of treatment sites.

At each visit study participants will be asked if they have experienced any adverse events which may have developed since starting the study medication, changes in their medications, and changes in any procedures. In addition, the study participant will complete another VAS at Week 16 to assess adverse events from using the study medication (add to appendix).

8.0 RANDOMIZATION PROCESS

There is no randomization process. This is an open-label pilot study.

9.0 APPLICATION OF STUDY CREAM:

Study participants will apply cream to face every other night After washing the face with cetaphil soap and patting it dry. A pea size amount of cream will be evenly distributed over the whole face.

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10.0 STUDY DESIGN

10.1 VISIT LOG:

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10.11 Two weeks prior to starting the application of Aldara

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- Informed consent will be obtained.
- Study participant demographic information will be obtained.
- Study participant will be asked to discontinue the use of all topical medications to the face for two weeks prior to starting study medication.
- Medical history, concurrent medication, and allergy history will be obtained from the study participant.
- Females of child-bearing potential will undergo a urine pregnancy test. If negative, participant will commence using study medication. If positive, participant will be exited from study.

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10.12 Day O (when the Aldara cream is dispensed)

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-
- VAS scale completed by patient and another by the physician to assess skin appearance.
-
- Color and ultraviolet photographs will be taken of face.
- 12 packets of Aldara will be given to each study participant. The application of the cream will be explained, as well as if there is any irritation the patient will be notified what to do.

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10.13 **Week** #2

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-
- Investigator will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet photographs will be taken of face.
- VAS scale completed by patient and another by the physician to assess skin appearance.

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Completion of study participant questionnaire and physician questionnaire.

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10.14 **Week** #4(this will be the first month of application, and we will be able to assess well for any irritation which is the most common side effect.

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- VAS scale completed by patient and another by the physician to assess skin appearance.
-
- Investigator will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet photographs will be taken of face.

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10.15 Week #8

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- Investigator will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet photographs will be taken of face.
- VAS scale completed by patient and another by the physician to assess skin appearance

10.16 Week #12

-
- VAS scale completed by patient and another by the physician to assess skin appearance
- Investigator will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
-
- Color and ultraviolet photographs will be taken of face.

10.17 Week #16

- Completion of study participant questionnaire and physician questionnaire.
- Study participant will complete VAS scale assessing skin appearance and VAS scale assessing side effects from using study medication.
- Investigator will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Females of child-bearing potential will undergo a urine pregnancy test.
- Color and ultraviolet photographs will be taken of face.
- There will be final recompilation of the data and the pictures which will be analyzed by an independent observer.

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Deleted: Females of child-bearing potential will undergo a urine pregnancy test.

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11.0 COMPLIANCE:

Participants will also be asked to return to the clinic for follow-up visits.

12.0 SAFETY ASSESSMENTS:

The safety of Aldara cream will be assessed by evaluation of the frequency, severity and duration of adverse events.

At the end of study medication use, the safety of Aldara will be determined by:

a) reports of any adverse events during the course of the study.

b) evaluation of post-treatment Visual Analog Scale (VAS) responses assessing adverse events.

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13.0 EFFICACY ASSESSMENTS:

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This study will evaluate the efficacy of Aldara cream for photoaged skin.

At the end of study medication use, the efficacy of Aldara will be determined by:

a) serial photography evaluated by blinded, independent (dermatologist) observer.
b) comparison of serial study participant and physician questionnaire responses pre- and post-treatment.
c) comparison of pre- and post-treatment Visual Analog Scale (VAS) responses assessing skin appearance.

14.0 PARTICIPANT DISCONTINUATION:

The Investigator may discontinue individual study participants from the study at any time. Study participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time from the study. The Investigator will provide a written report on the reason for discontinuation. If a study participant withdraws or is discontinued from the study before completion, every effort should be made to complete the scheduled visits.

A study participant may be removed from the study for the following medical or administrative reasons:

14.1 Adverse event

If a participant suffers an AE that, in the judgment of the Investigator, presents an unacceptable consequence or risk to the participant, the participant may be discontinued from further participation in the study.

14.2 Intercurrent illness

A study participant may also be discontinued from the study if, in the judgment of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements.

14.3 Administrative Discontinuation

A participant may be discontinued from the study for the following reasons:

Failure to return for follow-up visits

Reasonable efforts will be made to monitor the participants for compliance.

15.0 PROCEDURES IN CASE OF AN EMERGENCY:

Each study participant will be given information regarding emergency contacts. This information will contain numbers for the research staff and the doctor.

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16.0 PARTICIPANT INFORMATION:

All information pertaining to each study participant will be kept confidential. The records will be kept in the files of the Principal Investigator conducting this study at the UM Cosmetic Center located in the Cedars Medical Center, 1295 N.W. 14th Street, Suite K, Miami, FL. The records will be locked when not in use. The charts will be coded by study participant number and initials on the exterior of the study binders.

17.0 ETHICAL APPROVAL:

The University of Miami Institutional Review Board will review the study protocol, including study participant information and consent form. The study will not commence until full approval is received by the IRB.

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This will be an open label, pilot study of Aldara cream. Twenty participants with signs of photo-aging will be entered into the study. How is photoaging going to be determined? The study participants will be asked to discontinue the use of all topical medications to the treatment sites for two weeks prior to the study (This visit is 'the washout' and needs to be Day -2 weeks see section 10.0). On Day 0, the study participants will be provided with 12 packets of Aldara cream. Women of child-bearing potential will undergo a urine pregnancy test prior to receiving the study medication. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study.

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The study participant treatment sites will be evaluated on Day 0, Week 2, Week 4, Week 8, and Week 16 (what's the reason for this pattern?). At each visit, the study participant and Investigator will assess the appearance of XXXXX the following scale should be given a name and put in Appendix as #1) a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) telangectasias, and e) scaling. Each of these parameters will be graded on a 0-3 scale, 0= none, 1= mild, 2=moderate, 3=severe. Participants will also be evaluated for the presence of other photo-aged related lesions, such as actinic keratoses through what method and criteria?.

At each visit the study participants will have color and ultraviolet photographs taken of their face. The Canfield photography system will be utilized to maintain consistency. After Week 16, the photographs will be evaluated by a blinded independent dermatologist, comparing the study participants' photographs with their baseline photographs to assess the efficacy of the study medication on photo-aging. The independent observer will use a photo-aging scale (as above, scale given a name and put in Appendix as #2, using 0=none, 1=mild, 2=moderate, 3=severe.

At Day 0 and Week 16, study participants will complete a visual analog scale (VAS) (add to appendix) to assess the cosmetic appearance of treatment sites.

At each visit study participants will be asked if they have experienced any adverse events which may have developed since starting the study medication, changes in their medications, and changes in any procedures. In addition, the study participant will complete another VAS at Week 16 to assess adverse events from using the study medication (add to appendix).

EXHIBIT F

University of Miami

07-10-03 P04:41 IN

Interdepartmental Requisition Form

IR REFERENCE: IR

DOCUMENT REFERENCE NO.: DR 938784

Credit Account Number:

TYPE OR PRINT

NO ENVELOPE NECESSARY · THIS IS A SELF MAILING FORM
ADDRESS - FOLD - STAPLE - MAIL

	NAME/DEPARTMENT	CAMPUS	BUILDING	ROOM	LOCATOR CODE
TO:	IRB	MED	JMT		
FROM:	UMCC/DERM	MED	CEDARS	K	R-250

DESCRIPTION	QUANTITY	UNIT PRICE	ACCOUNTS TO BE CHARGED				CREDIT	
			ACCOUNT NO.	*OBJECT	I	AMOUNT	*OBJECT	I
COMPLIANCE FEE								
NEW PROTOCOL								
PHYSICIAN INITIATED			301713			350.00		
ALDARA $								

DERMATOLOGY ADMINISTRATION

APPROVED Martinez 7/11/03

↑ FOLD UP — FOLD UP ↑

DELIVER TO: Name _____ Campus _____ Locator Code _____

Building Room No. Delivery Point

FOR FURTHER INFORMATION CONCERNING THIS REQUEST, PLEASE CONTACT

NAME Joy M. Bryde 7/10/03 PHONE 324-7546

Printed or Typed Name of Authorized Signature		Dept. Head or Dean Approval (if required)	Date
Authorized Signature	**Date**	**Budgetary Approval**	**Date**
[signature]	7/11/03		

FA-2 331217
5/92

Instructions on reverse side

ORIGINAL (white), DELIVERY (yellow), DEPARTMENTAL (pink)

University of Miami · Office of Research
P.O. Box 016960 · Miami, FL 33101 (R-64)
Tel. 305-243-6415 · Fax. 305-243-3594
http://www.miami.edu/research

Office of Research Use Only:
Date Received: _____
Research Protocol #: _____

RESEARCH COMPLIANCE FEE TRANSMITTAL FORM

INSTRUCTIONS:
1. This form must be typed and must accompany all new research protocol submissions.
2. All new research protocols are subject to the Research Compliance Fee of $350.00. The only exceptions to this rule are:
   a. Government-sponsored research studies.
   b. Research studies not subject to Full IRB Review.
3. If applicable, attach an IDR for $350.00 made payable to the Office of Compliance.
4. Submit this form and all applicable material to the Human Subjects Research Office (HSRO), 1500 NW 12th Avenue, Suite 1000, Miami, FL 33136.

I. Research Protocol Information

A. Principal Investigator

Name: Leslie Baumann, MD Title: Associate Professor
Department: Dermatology Division: Cosmetic Dermatology
Email Address: lsb@derm.net Tel.: 305-324-7546 Fax: 305-324-9249
Campus Address: Cedars Medical Center, 1295 NW 14th St. Ste. K, Miami, FL 33125 Mail Code: R-250

B. Title of Protocol:

Pilot Study of the Use of Aldara(TM) for the Treatment of Photoaging

C. Sponsor: None

D. UM Proposal Number: N/A

E. UM Account Number: 301713

II. Research Compliance Fee:

A. ☑ An IDR for $350.00 is attached. IDR# 938784

OR

B. ☐ Research is exempt from the research compliance fee for one of the following reasons:
- ☐ *Research is sponsored by a federal, state or local government agency.*
- ☐ *Research falls under either the exempt or expedited review categories and is therefore not subject to Full IRB Review.*

III. Signature:

Principal Investigator's Signature Leslie Baumann, MD (Print Name) 7/14/03 (Date)

UNIVERSITY OF MIAMI
HUMAN SUBJECTS RESEARCH OFFICE
(HSRO)
Locator: M-809
Phone: (305) 243-3195

IRB PROTOCOL REVIEW

TRANSMITTAL

INSTRUCTIONS: This form must accompany all submissions for IRB PROTOCOL REVIEW. **To avoid processing delays, please ensure that an IDR or appropriate authorization of exemption or waiver is attached.**

PROTOCOL IS:

- [X] NEW
- [ ] CURRENT,#_____

TYPE OF SUBMISSION

- [ ] AMENDMENT
- [ ] CONTINUING REPORT
- [ ] FINAL REPORT
- [ ] ADVERSE EVENT
- [ ] OTHER:_____ (Please describe)

PROCESSING FEE

(Applicable to New Protocol, Amendment, Continuing Report)

- [ ] IDR #_____ for $_____ is attached
- [X] EXEMPT...Please check one the following applicable reasons:
  - ( ) Sponsor is Federal, State, or local government agency
  - ( ) Sponsor is private but not a pharmaceutical/device company
  - ( ) Research effort is not funded by sponsor
  - (X) Sponsor is ONLY providing the drug or device
  - ( ) Written authorization (email/fax/letter) from the Research Administration Office is attached
- [ ] WAIVED... Written authorization (email/fax/letter) from the Vice Provost for Research is attached

You will be notified within one business day of receipt if additional information is necessary to appropriately process your submission. **Please provide an email address (or fax number if you do not have access to an email system) for this purpose:**

jbryde@derm.net

SIGNATURE OF PRINCIPAL INVESTIGATOR: _____ 7/11/03 Date

FOR HSRO USE ONLY

DATE RECEIVED:_____

SUBMISSION IS: [ ] Complete [ ] Incomplete

AMENDMENT IS: [ ] Major [ ] Minor

FINAL	MAJ AMEND	MIN AMEND	ADV EVENT	CONT REPT	INF	GOVT AGCY	PRIV SRC	NONE	CHARGE	WAIVE	EXEMPT

ASSIGNED TO COORDINATOR: _____

LOGGED BY:_____

ASSIGNED TO COMMITTEE:_____

LOGGED DATE:_____

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University of Miami · Human Subjects Research Office (HSRO)
P.O. Box 016960 · Miami, FL 33101 (M-809)
Tel.: 305-243-3195 · Fax: 305-243-3328 · http://www.miami.edu/research-irb

HSRO USE ONLY:
DATE RECEIVED: _____
APPLICATION #: _____

MEDICAL SCIENCES RESEARCH PROTOCOL FORM
FOR FULL IRB OR EXPEDITED REVIEW

Instructions: This form must be typed. Please complete this form, print it out and submit the original with the required signatures to the IRB. Please also submit fifteen (15) copies with the original to the IRB.

1. **TITLE OF THE STUDY:**
Pilot Study of the Use of Aldara™ (imiquimod 5%) for the Treatment of Photoaging

2. **TYPE OF REVIEW REQUESTED**: Please check one.
☒ Full IRB Review
☐ Expedited Review: Under what category, please state the category number:
(Please visit the IRB website for a listing of the expedited categories)

3. **STUDY PERSONNEL: ALL PERSONNEL LISTED ON THE STUDY, REGARDLESS OF THEIR ROLE, MUST BE IRB-CERTIFIED.**

(a) **PRINCIPAL INVESTIGATOR**: A full-time University of Miami (UM) or Jackson Health System (JHS) employee who assumes full responsibility for the study.

Name:	Leslie Baumann, MD	**Telephone Number:**	(305) 324-7546
Title:	Director	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	lsb@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250

(b) **SUB-INVESTIGATOR(S) OR CO-INVESTIGATOR(S)**: All Sub- or Co-Investigators involved in the study must sign and date this application. **If there are more sub- or co-investigators than spaces available, please list them on a separate sheet and attach the sheet to this application.**

Name:	Lucy K. Martin, MD	**Telephone Number:**	(305) 324-7546
Title:	Research Fellow/Sub-Investigator	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	lmartin@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250

Signature: Lucy K. Martin

Name:		**Telephone Number:**	
Title:		**Fax Number:**	
Department:		**E-mail Address:**	
Division:		**Mailing Locator Code:**	

Signature: _____

(c) **COLLABORATOR(S)**: Individuals not affiliated with the University of Miami. **If there are more collaborators than spaces available, please list them on a separate sheet and attach the sheet to this application.**

Name:	**Telephone Number:**
Title:	**Fax Number:**
Address:	**E-mail Address:**

Name:	**Telephone Number:**
Title:	**Fax Number:**
Address:	**E-mail Address:**

(d) **KEY PERSONNEL:** Other than those listed above, list the key personnel involved in this study: Key personnel are defined as individuals who contribute in a substantive way to the scientific development or execution of a project, whether or not they receive compensation from the grant supporting that project. **If there are more key personnel than spaces available, please list them on a separate sheet and attach the sheet to this application.**

Name:	Joy Bryde, MSW	**Telephone Number:**	(305) 324-7546
Title:	Dir. of Research/Sr. Res. Assoc.	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	jbryde@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250
Name:	Laura Black, MA, MPH	**Telephone Number:**	(305) 324-7546
Title:	Senior Research Associate	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	lblack@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250
Name:	Franshely Calero	**Telephone Number:**	(305) 324-7546
Title:	Research Staff	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	fcalero@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250
Name:	Esperanza Welsh, MD	**Telephone Number:**	(305) 243-4472
Title:	Dermpath Fellow	**Fax Number:**	(305) 243-6191
Department:	Dermatology	**E-mail Address:**	esperanzaw@hotmail.com
Division:	Dermatopathology	**Mailing Locator Code:**	R-250

(e) **CONTACT PERSON(S):** Personnel you wish to be included in correspondence related to this study e.g. study coordinator.

Name:	Joy Bryde, MSW	**Telephone Number:**	(305) 324-7546
Title:	Dir. of Research/Sr. Res. Assoc.	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	jbryde@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250
Name:	Laura Black, MA, MPH	**Telephone Number:**	(305) 324-7546
Title:	Senior Research Associate	**Fax Number:**	(305) 324-9249
Department:	Dermatology	**E-mail Address:**	lblack@derm.net
Division:	Cosmetic Dermatology	**Mailing Locator Code:**	R-250

4. **PERFORMANCE SITE(S):**

(a) Is this a multi-center study? ☐ Yes ☒ No

(b) Will this study involve any performance sites outside of the United States of America? ☐ Yes ☒ No

If yes, what country or countries?

(c) List all sites at which Investigators and Collaborators will engage in protocol activities.

Institution	Location	Address
UM Dermatology	UM Cosmetic Center	Cedars Medical Center South Building, Suite K 1295 NW 14th St. Miami, FL 33125

5. **Proposed Start Date at UM:** 8/25/2003
6. **Proposed Termination Date:** 3/31/2004 (Unknown is not an acceptable answer)

7. **Name of Funding Agency:** N/A

   Date Submitted to Funding Agency:
   (For NIH grants, a copy of the award letter must be submitted prior to IRB review)

8. **ADDITIONAL COMMITTEE REVIEW:**
   Is this protocol subject to review by another Committee? ☐ Yes ☒ No
   If "Yes", please check all that apply:

   ☐ Cancer Protocol Review Committee (PRC)
   ☐ Human Use Radioisotope Committee
   ☐ Institutional Bio-Safety Committee (IBC)
   ☐ General Clinical Research Center (GCRC)
   ☐ Other:

   Include the appropriate documentation of approval from these committees.

9. Study Coordinating Center or Cooperative Study Group:

N/A

10. **PROJECT OBJECTIVES:**

The primary objectives of this study are to evaluate the safety and efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photodamaged skin.

11. **METHODS AND PROCEDURES:** (Give detailed information and describe the consent process)

BACKGROUND INFORMATION

Aldara™ (Imiquimod topical 5%) is an FDA-approved topical therapy for the treatment of genital warts. Imiquimod topical 5% induces the production of several cytokines such as interferon, which is known to aid in the elimination of viral infections such as the one that causes by genital warts. These cytokines might also have an effect on photoaging.

It has been shown in case series that Aldara™ (imiquimod 5%) cream also plays a role in the elimination of skin cancers such as basal cell carcinomas through the induction of cytokines. While the anticarcinogenic effects are beyond the scope of this pilot study, it is important to determine whether this compound can be used for photoaging without major side effects. In our practice, we have used Aldara™ (imiquimod 5%) for the treatment of basal cell carcinomas and have noted an improvement of the surrounding photoaged skin.

Alternative treatments for photoaging include topical retinoids such as Retin-A®, Accutane®, and Tazorac®, and resurfacing treatments such as chemical peels and dermabrasion. However, retinoids can cause redness, flaking, and irritation of the skin, and cannot be tolerated by some patients. Skin resurfacing treatments involve injury to the epidermis. This study will assess the efficacy and safety of topical Aldara™ (imiquimod 5%) cream for the treatment of photodamaged skin.

STUDY DESIGN

This study will be an open-label, pilot study to examine the safety and efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photoaging. There will be no randomization procedure for this study. Twenty participants will be enrolled. Participants will be assessed clinically two weeks prior to beginning treatment with the study medication (Week -2);

participants who meet the study criteria will be asked to discontinue the use of all topical medications on the treatment sites for two weeks prior to using the study medication. Women will undergo a urine pregnancy test prior to receiving the study medication. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study. On Day 0, the study participants will be provided with enough packets of the study cream for 2 weeks of every other day application (1 packet = 1 application). At the Week 2 visit, participants will be assessed for tolerability of gel and usage will either stay the same, be increased to once daily application, or be decreased to every third day application. Further study medication will be distributed at this time. Participants will be asked to apply the study cream to the face and will be followed for a period of 16 weeks.

METHODS

Study Entry Procedures
Prospective subjects, as defined by the inclusion and exclusion criteria, will be considered for entry into this study. The study will be reviewed with the potential participant and informed consent will be obtained before any study-related procedures are conducted, including photographs.

Once enrolled, the study participants will be asked to discontinue the use of all topical medications to the treatment sites for two weeks prior to using the study medication. Women will undergo a urine pregnancy test. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study. Acceptable forms of birth control include: abstinence from heterosexual intercourse, birth control pills, patch, or implant; depo-progesterone injections; barrier contraceptives such as a condom, diaphragm, and spermicidal foam or jelly (combination of at least two of these methods; intrauterine device (IUD); or surgical sterilization (hysterectomy or tubal ligation).

Study Visit Procedures
Participants who are enrolled in the study will return 2 weeks later for the Day 0 visit. Female participants will undergo a urine pregnancy test. Women with a positive pregnancy test at Day 0 will be discontinued from the study.

On Day 0, the study participants will be given enough packets of study cream for 2 weeks of every other day application (1 packet = 1 application). After review with the research team, the participants will also be provided with an instruction sheet detailing application procedures. At this visit, participants will be instructed to begin using the study medication every other day. The study participant and investigator will assess the safety and efficacy of the study medication using the procedures described below.

Follow-up evaluations will occur at visits on Week 2, Week 4, Week 8, Week 12, and Week 16. This schedule has been chosen in order to assess adverse events quickly and to have a monthly evaluation of treatment response. At the Week 2 visit, participants will be assessed for tolerability of the study medication and usage will either stay the same, be increased to once daily application, or be decreased to every third day application. Further study medication will be distributed at this time. At each follow-up visit, the study participant and investigator will assess the safety and efficacy of the study medication using the procedures described below. If the participant uses more than the initial packets of study medication than given, more packets will be dispensed as needed, and the number of packets given will be recorded.

Procedures to occur
Efficacy
- Visioscan® Measurements

At each visit, Visioscan® measurements will be taken in order to determine the texture of the facial skin. The Visioscan® measures 4 parameters: smoothness, roughness, scaliness, and wrinkles. Using an eyebrow pencil, which is easy to wash off, a rectangle will be drawn on the participant's face to mark the site for camera placement. A circular sticker will be placed over the rectangle, the hand-held camera will be placed over the circle, and a close-up picture of the skin will be taken.

- Tewameter® Measurements

Tewameter® measurements will be taken at each visit in order to quantify water loss from facial skin. A double-sided sticking strip will be placed on the participant's skin at the measurement site. The probe will be affixed to the other side of the sticking strip. Measurements will be recorded for 30 seconds.

- Investigator Assessment

At each visit, the investigator will evaluate the facial skin using a questionnaire. The Investigator Questionnaire (Appendix A) will assess the appearance of a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) spider veins, and e) brown pigmentation on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe). Participants will also be clinically evaluated for the presence of other photoaging-related lesions, such as actinic keratoses. The number of these lesions will be counted.

- Participant Assessment

At each visit, participants will evaluate their facial skin using the same scale as the physician. The Participant Questionnaire (Appendix B) will also assess the appearance of a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) spider veins, and e) brown pigmentation on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe). In addition, at Day 0 and Week 16, participants will complete visual analog scales (VAS) assessing the cosmetic appearance of the treated sites (Appendix D).

- Serial Color Photography/Blinded Independent Dermatologist Assessment

At each visit, the study participants will have color and ultraviolet photographs taken of their face (Canfield facial camera). At the end of the study, the photographs will be evaluated by a blinded independent dermatologist, comparing the study participants' photographs with their baseline photographs to assess the efficacy of the study medication. The Independent Dermatologist Questionnaire will employ the same assessment scale as that used by the investigator (Appendix C), except that the tactile roughness assessments will be eliminated.

Safety

At each visit study participants will be asked if they have experienced any adverse events that may have developed since starting the study medication (number, frequency and severity will be recorded), changes in their medications, and changes in any procedures. At the Week 16 visit, participants will complete a VAS scale (Appendix D) to assess the adverse events associated with treatment.

Study Exit

Participation will be considered completed after use of the cream for 16 weeks.

12. **RISKS**: (Give detailed description of the physical, psychological, social and economic/financial risks to the participants)

All medications have side effects and these can sometimes be unforeseen. In this study, Aldara™ (imiquimod 5%) is an investigational treatment for the improvement of photoaging, and all of its possible side effects are not known. In previous studies, enrolled participants reported some side effects which participants may experience.

Application Site:

Likely (Happens to 20 – 60%): Erythema (redness), erosion (skin loss), excoriation (scraping)/flaking, itching

Occasional (Happens to 5 – 20%): Edema (swelling), induration (hardness), ulceration (deeper skin loss), scabbing, burning, pain, fungal infection

Rare (Happens to < 5%): Vesicles (tiny blisters), soreness, hypopigmentation (light spots), hyperpigmentation (dark spots), irritation, rash, sensitivity, stinging, tenderness

Remote Site:

Rare (Happens to < 5%): Erythema, ulceration, edema, erosion, induration, excoriation/flaking, bleeding, burning, itching, pain, tenderness, tinea cruris (a fungal infection)

Systemic (Whole Body):

Occasional (Happens to 5 – 20%): Headache

Rare (Happens to < 5%): Influenza-like symptoms, myalgia (muscle aches), fatigue, fever, diarrhea

Follow-up information on the hypopigmentation (light spots) and hyperpigmentation (dark spots) experienced by previous study participants suggests that these skin color changes may be permanent.

In addition, if participants have precancerous lesions or skin cancers on their face, tehy will experience redness and possible erosions in the areas of those cancerous lesions. These effects have been seen in studies for Aldara™ (imiquimod 5%) for the treatment of skin cancer. The redness and erosions resolve when participants stop using the study medication, but continued use of the study medication may result in elimination of the precancerous lesions or

cancer. Participants should continue to use the study medication unless they feel that the redness and erosions are not tolerable.

Participants with sensitivity to adhesives may experience a localized skin reaction to the adhesive strips used for Visioscan® and Tewameter® measurements.

The study medication must be used only by the participant and should be kept out of the reach of children or others of limited capacity to read or understand.

Imiquimod topical 5% cream is not recommended for use by patients with a known hypersensitivity to it or to any of the ingredients of the product. The photosensitivity of the product is unknown, so participants should minimize the exposure of treated areas to sunlight and sunlamps. Participants should also use the provided sunscreen while using the study medication. Although Aldara™ (imiquimod 5%) has not been associated with birth defects, fetal harm is unlikely but possible. This medication has been shown to have minimal systemic absorption. No interference with laboratory tests has been observed. Beneficial effects from the study cream are possible after discontinuation of cream use, but it is unknown.

Women: In addition, if a participant is pregnant or becomes pregnant, there may be a risk of spontaneous abortion or fetal malformation. A participant must not enter the study if she is breast-feeding a baby or intends to try to become pregnant. The effects of imiquimod on an unborn baby have not been studied and are unknown. The risk that it could cause a miscarriage or affect the baby's development is not known. Participants will not be allowed to enter the study or to receive the study treatments if their pregnancy test is positive. Participants must use adequate contraceptive precautions during the study. Acceptable forms of birth control for this study include (1) use of oral contraceptives for at least 1 month prior to treatment and for the duration of the study, OR (2) the use of two forms of contraception (i.e. condoms plus spermacide), (3) be surgically sterile or post-menopausal for at least 1 year, OR (4) abstinence from heterosexual sex. If a participant has any suspicion that she is pregnant, or should a participant become pregnant during the course of this study, she must inform Dr. Baumann immediately.

If participants experience any illness or discomfort during the study, they should notify one of the study doctors. One of the study doctors will then evaluate them to determine if they should continue in the study.

Participation in this medical research study may involve risks from the medications that are currently unforeseeable or unknown.

13. SUMMARY OF RESULTS OF THE PRELIMINARY INVESTIGATIONAL PHASE OF USING THE DRUG OR DEVICE OR PRELIMINARY RESULTS FROM THE INVESTIGATOR'S GROUP: (Only if using investigational drugs or device):

Off-label use of approved drug

14. **HUMAN SUBJECTS:**

(a) Number of Subjects to be enrolled in the entire study: 20
(b) Number of Subjects to be enrolled at the University of Miami: 20
(c) What is the anticipated percentage of the male subjects? 25%
(d) What is the anticipated percentage of the female subjects? 75%

(e) Age Range of Subjects:

0 – 6:		(Parental Consent Required)
7 -17:		(Parental Consent and Child Assent Required)
18 – 65:	X	
65 and older:	X	

(f) Advertising for Study Subjects: ☒ Yes ☐ No
(If yes, you must submit details and examples of all forms of recruitment for approval)

(g) **Explain Recruitment Procedures:**

Please Note: If you intend to recruit subjects with whom you do not have and have not had a treatment relationship, please indicate whether:

1. You will rely on the individual's healthcare providers to contact them on your behalf, ***or***
2. You will provide verification that the health care provider(s) that has or had a direct treatment relationship with the patient(s) has or have agreed to allow contact with such patients for the proposed research opportunity, ***or***
3. You are requesting a "partial" waiver of authorization to enable you to contact these individuals directly. If you are requesting a partial waiver of authorization, complete and attach to this application a ***"Request for Partial Waiver of Authorization" (Form F)***.

Other: direct recruitment through ads and flyers

(h) **Expense to Subjects** (please give details):

Participants will be responsible for opportunity costs such as parking.

(i) **Payment to Subjects** (please give details):

None

Compensation for Injury: You are required to advise the research subject of any funds available to pay for the treatment of any injuries caused by research. If the purpose of the study is to evaluate a drug, device, or other intervention on behalf of a sponsor, the sponsor must generally provide reimbursement for the cost of treating any injuries or adverse events experienced by the research subjects. Please provide full information together with supportive documents to the Office of Research Administration, Tom Gill at 305-243-6232.

(j) **Subject Characteristics:**

☒ Normal Healthy Volunteers ☐ Inpatients ☒ Outpatients ☐ Deceased Subjects

(k) **Subject Population:** (Please check all that apply)

☐ Feti
☐ Aborti
☐ Cognitively Impaired/Mentally Retarded
☐ Prisoners
☐ Traumatized and Comatose Patients
☒ Other: Photoaging on facial skin
☒ Elderly
☐ Pregnant Women
☐ Children under 18 years of age
☒ Employees (UM/JMH)
☒ Students (UM/JMH)
☐ Psychiatric disorders

Federal regulations have established guidelines for the inclusion of women, minorities, and children in research involving human subjects, whether or not it is supported by NIH. Please check those you are excluding:

☐ Women ☐ Minorities ☐ Participants under the age of 21

Please provide a justification for the exclusion:

15. PRIVACY AND CONFIDENTIALITY OF DATA AND RECORDS

Note: This Section must be completed regardless of the nature of the research (e.g., clinical research, research with existing data, research with biological materials or tissues), whether the research is exempt from IRB review under federal human subjects regulations, or whether the prospective subjects are living or deceased individuals. If you have any questions regarding the information required by these sections, please see the HIPAA Privacy Procedures for Research section of the IRB Policies and Procedures.

A. As part of the proposed research, will you or anyone who assists you:

(i) review medical records, billing records, or other patient information maintained by or on behalf of UM and/or JHS for purposes of developing a research protocol or identifying potential research participants; *or*

(ii) conduct research involving UM and/or JHS patients or using medical records, billing records, or other patient information maintained by or on behalf of the UM and/or JHS; *or*

(iii) create health information that may be used to provide a research subject with medical care/treatment at UM or JHS;

regardless of whether you act on your own behalf, for another Investigator, or on behalf of a third party (e.g., for persons without admitting privileges at the Covered Entity or for a medical device or pharmaceutical company or contractor).

[**NOTE:** For purposes of item (iii), "creating health information" consists of collecting or creating information that will be used in diagnosing a condition and/or providing treatment as part of the research study. Collecting a medical history from the study participant without placing the information in or accessing their medical records is not generally considered "creating health information". Conducting tests or evaluations not meant to be used for diagnosis or treatment, but rather, for study screening or research information/background purposes is not generally considered "creating health information".]

☒ Yes. ***Continue to the next question B.***

☐ No. ***Provide an explanation of what information is to be accessed or collected for the study and why you are not creating "health information".***

Do not complete the rest of this section. Proceed to question 16.

B. To which of the following identifiers about subjects (or their relatives, household members, or employers) *might* access be needed during the course of the proposed research?

Check all that apply:

☒ Names
☒ Geographic subdivisions smaller than state (e.g., street address, city, five digit zip code, county)
☒ Months or specific dates (e.g., birth date, admission date, month of discharge, date of death)
☐ References to age 90 or older *or* references to dates or years indicative of age 90 or older
☒ Telephone numbers
☒ Fax numbers
☒ E-mail addresses
☒ Social security numbers
☐ Medical record or prescription numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ Medical device identifiers or serial numbers
☐ Biometric identifiers (e.g., finger or voice prints)
☒ Full face photographic images or comparable images
☐ Web Universal Resource Locators (URLs)
☐ Internet Protocol (IP) address numbers
☐ Certificate or license numbers (e.g., driver's license numbers)
☐ Vehicle identifiers or serial numbers (e.g., license plate numbers, VINs)
☐ Linkage codes (to permit re-identification or longitudinal tracking) derived from or related to any of the above.

-OR-

☐ By checking this box, I confirm that access to the identifiers listed above are not required or anticipated.

C. Indicate below whether you will obtain subjects' authorization to use and disclose their health information or whether there is an applicable exception to the authorization requirement.

Check all that apply:

Authorization

☒ A signed, written **authorization** to access, use, and disclose protected health information will be obtained from each subject (or their legal representative). ***Prepare and attach a proposed Authorization to Use and Disclose Health Information using the IRB's pre-approved template (Form B).***

Limited Data Set/Data Use Agreement

☐ I need only a **limited data set** of information for this protocol and wish to enter into a Data Use Agreement with the University and/or JHS as a condition of obtaining from the University and/or JHS and using this information.

A limited data set is required from: ☐ University ☐ JHS ☐ Both

Prepare and attach a proposed Data Use Agreement for each place from which you will obtain a limited data set using the pre-approved template (Form C) and include a list of the data fields you will need in the limited data set. In addition, choose one of the following:

☐ I would like the University/JHS to create the limited data set for me.

☐ A member of the University or JHS workforce will create the limited dataset.

☐ I would like a third party which has entered into a business associate agreement with the University to create the limited data set for me. ***Attach a copy of the business associate agreement between the University and the third party.***

Waiver of Authorization

☐ I am requesting a **waiver of authorization** (in whole or in part). To assist the IRB in considering this waiver request, please address **each** of the following questions:

(a) Why would it be impractical to conduct the proposed research without a waiver?

(b) Why would it be impractical to conduct the proposed research without access to and use of the identifiers selected in item B, above?

(c) Describe your plan to protect participant-identifying information from improper use and disclosure. (If information will be stored in electronic databases, describe how this system will be protected from unauthorized users and state how long this database will be kept.)

(d) Describe your plan to destroy or to return to the University or JHS participant-identifying information at the conclusion of the research. If some or all of the identifying information will need to be retained, explain why.

(e) Federal law prohibits the re-use or disclosure to a third party of any participant-identifying information created or obtained pursuant to a waiver of authorization except: as required by law; for oversight of the research; or for other research for which individual authorization or a new waiver of authorization is obtained. **By initialing here, I confirm that I agree to abide by these limitations: _____.**

(f) If the proposed research involves access to and analysis of existing protected health information maintained by or on behalf of the University or JHS (i.e., it is not clinical research), explain why use of a Limited Data Set is not appropriate.

Certification for Research with Decedents' Information

☐ The proposed research involves access to and analysis of protected health information concerning **deceased individuals** for which neither authorization of legal representatives, waiver of authorization, nor a Limited Data Set will be sought.
Attach an Investigator's Certification for Research with Decedents' Information (Form D).

16. **RESIDUAL SAMPLES:**

(a) Does this research include or consist of storing tissue, blood or other biological materials at UM or other sites for other than routine testing? ☐ Yes ☒ No

If yes, specify the kind of material (e.g. blood, cell lines, skin tissue, liver tissue, etc.):

(b) Will the stored samples be used for genetic research? ☐ Yes ☐ No
If yes, a genetic consent form will be needed.

(c) State briefly the kind of research to be conducted:

(d) Will the samples be linked to their patient/subject source by a unique identifier or code? ☐ Yes ☐ No

If yes what kind:

(e) Will the samples be stored with any protected health information? ☐ Yes ☐ No

If yes, what kind?

(f) Will the samples or the information in them be shared with any non-UM/JHS organizations? ☐ Yes ☐ No

If yes, with whom:

(g) Will the samples or the information be kept by or transferred to any non-UM/JHS organizations?
If yes, by whom or to whom?

(h) Will the information be stored in an electronic database? ☐ Yes ☐ No

If yes, will the database be maintained at UM or JHS: ☐ Yes ☐ No

If no, who will keep or maintain the database?

(i) Can the subject decide not to participate in the genetic research and still participate in the study?

☐ Yes ☐ No

(j) Will the transportation and storage of the residual samples place anyone at a health risk?
☐ Yes ☐ No

If yes, please explain:

The informed consent document should adequately describe to the study participants any of the above types of activities that will be taking place with respect to the use or transfer of specimens or information obtained form them during the course of the research.

17. **SAFETY MONITORING BOARD:**

For Phase I and Phase II clinical trials, investigators must submit a detailed plan of the data and safety monitoring as part of their research application. At a minimum, all monitoring plans must include a description of the reporting mechanisms of adverse events to the IRB, FDA, and the NIH. The overall elements of the monitoring plan may vary depending on the potential risks, and the nature of the trial.

Provide the data and safety monitoring plan if you are conducting a Phase I and/or Phase II clinical trial:

N/A

For the Phase III clinical trials a Data Safety Monitoring Board (DSMB) is required for multi-site clinical trials involving interventions that entail potential risk to the participants. Information on DSMBs can be found in the NIH web site: http://grants.nih.gov/grants/guide/notice-files/not98-084.html

If you are conducting a Phase III clinical trial, provide a description of the mechanisms you have put in place for establishing a DSMB:

N/A

Please note that reports issued by Data Safety Monitoring Boards (or similar entities), whether within or outside the University, must also be submitted to the IRB within five (5) working days of receipt by the Principal Investigator.

18. **INFORMED CONSENT:**

A. ***Non-English Speaking Subjects:***

If it is anticipated that non-English speaking subjects will participate in the study, a translated written consent form must be used and the consent interview must be conducted in the same language as that of the translated written consent. The IRB must approve the written translation.

(i) Do you plan to include non-English speaking Hispanics subjects? ☒ Yes ☐ No

If "Yes", name of person obtaining informed consent from the subject(s): Leslie Baumann MD; Lucy K. Martin, MD; Laura Black MA, MPH; Franshely Calero

If "No", please explain why:

(ii) Do you plan to include Créole, speaking subjects? ☒ Yes ☐ No

If "Yes", name of person obtaining informed consent from the subject(s): Official translator will be obtained if participant's preferred language is Creole.

If "No", please explain why:

(iii) Do you plan to include non-English speaking subjects who speak languages other than Spanish or Creole?
☐ Yes ☒ No

If yes, what language:
If yes, name of translator of written consent form:

B. ***Documentation of Consent Form:***

☒ A signed consent form for each participant in this study will be obtained. Attached is a copy of the consent form.

THE INVESTIGATOR MUST RETAIN THE ORIGINAL IN HIS/HER FILE AND PLACE A COPY IN THE SUBJECT'S MEDICAL RECORDS/HOSPITAL RECORDS/STUDY RECORDS. A COPY MUST BE GIVEN TO THE SUBJECT.

If you are using JMH as a performance site, the consent form must be typed on the JMH C-640 Form.

C. ***Obtaining Consent:***

It is the Principal Investigator's responsibility to:
1. Explain the consent form to the subjects.
2. Determine that subjects fully understand the research protocol
3. Obtain the subject's signature.

If the investigator will not be the person obtaining consent, please identify the person who will and justify how that person is qualified to do so. This person must be IRB certified. If someone else replaces this person, the IRB needs to be notified immediately.

☒ Investigator ☐ Other Personnel

Print Name: Lucy K. Martin MD Title: Sub-Investigator
Justification:

Dr. Martin is experienced in participant enrollment and familiar with the protocol, study procdures, and techniques involved.

☐ Investigator ☒ Other Personnel

Print Name: Joy Bryde MSW; Laura Black MA, MPH; Franshely Calero Title: Research Staff
Justification:

Ms. Bryde, Ms. Black, and Ms. Calero are experienced in participant enrollment and familiar with the protocol, study procdures, and techniques involved.

D. ***Waiver of Consent:***

☐ If you are requesting a waiver of informed consent you need to justify each of the following:

(a) The research involves no more than minimal risk to the subjects:
Justification:

(b) The waiver or alteration will not adversely affect the rights and welfare of the subjects:
Justification:

(c) The research could not practicably be carried out without the waiver or alteration:
Justification:

(d) Whenever appropriate, the subjects will be provided with additional pertinent information after participation:
Justification:

19. **RECORDKEEPING:**

(a) State where the records pertaining to this protocol will be kept, including building and room number, how they will be secured and who will have access to these records:

Records will be kept in the files of the Principal Investigator conducting the study at the UM Cosmetic Center, located in the Cedars Medical Center, 1295 NW 14th St., Suite K, Miami, FL. The files will be locked when not in use. Access will be limited to the research staff.

(b) Describe the provisions which have been made for preservation of anonymity and confidentiality in the transmittal of data:

The records will be locked when not in use. Participant charts will be coded by study participant numbers on the exterior of the study charts.

20. **STUDY DRUGS:**

The Principal Investigator assumes responsibility for the maintenance, supervision, and administration of the drug(s).

You must submit three copies of the complete drug brochure for each investigational drug and three copies of package inserts for approved drugs.

(a) This project involves the use of: ☐ Investigational Drug(s) ☒ Approved Drug(s)

(b) Off-label use of marketed drug(s): ☒

If this is an off-label use of a marketed drug(s), please describe the uses for which the drug(s) is(are) currently approved:

Topical treatment of external genital and perianal warts/condyloma acuminata.

(c) Is the protocol investigator generated? ☒ Yes ☐ No

(d) This study is: ☐ Phase I ☐ Phase II ☐ Phase III ☒ Other pilot study

(e) **Drug Name(s):**

Generic	Brand	IND# (If Applicable)
Imiquimod 5% cream	Aldara™	

(Attach another sheet to list more drugs if necessary)

(f) Where will the drug(s) be stored? (Building, Room#):

UM Cosmetic Center, Cedars Medical Center, 1295 NW 14th St., Suite K, Miami, FL

(g) Who will supply/produce the drug?

3M Pharmaceuticals

(If the drug or product is being produced for the study purpose, adequate documentation and justification must be provided regarding the source of the drug or product, the fact that it has been produced in conformance with applicable standards, laws and regulations, and that it is fit for human use)

(h) How will the drug be secured?

Drug will be kept in a locked cabinet; access will be restricted to the personnel listed below.

(i) What is the justification for the drug not being held in a UM/JMH/VA pharmacy?

Medication needs to be immediately available to study investigators and research staff.

(j) How will the drug(s) be handled after the study is finished?

Excess packets will be returned to the manufacturer.

(j) If the drug is not stored in a pharmacy, who has access to the drug(s)? Please state each person's name and title.

Leslie Baumann, MD	PI
Lucy K. Martin, MD	Sub-PI
Joy Bryde, MSW	Key Personnel
Laura Black, MA, MPH	Key Personnel

(k) If the drug is not dispensed by a pharmacy, who has authorization to dispense the drug(s)? Please state each person's name and title.

Leslie Baumann, MD	PI

(l) Who has authorization to administer the drug? Please state each person's name and title.

N/A

(m) How will the investigator monitor drug inventories?

A drug inventory and usage log will be kept and reviewed by Dr. Baumann on a monthly basis.

If this research involves contact with nurses and staff that are not part of the Investigator's research team, you must complete the JMH/UM INVESTIGATIONAL NEW DRUG FORM. The form can be obtained from the IRB website at: http://www.miami.edu/UMH/CDA/UMH_Main/1,1770,6603-1,00.html

21. **STUDY DESIGN:**

The project involves the use of the following (check all that apply):

☐ Placebo ☐ Single Blind ☐ Double Blind ☐ Control Group ☒ Other

22. **INVESTIGATIONAL DEVICES:**

(a) Name of Investigational Device: N/A
(b) Investigational Device Exemption (IDE) Number:

If there is no IDE, under what category is this device exempt:

If the Investigator or Sponsor is requesting exemption as a non-significant risk device, adequate documentation and information must be provided for the IRB to make such a determination.

FINANCIAL CONFLICT OF INTEREST:

Investigators signing this form certify that none of the individuals named in the proposed protocol (or their spouse or dependent children) have a financial interest in the sponsoring entity or any organization involved in this project or in the article(s), product(s), drug(s) or device(s) that may be used or involved in the study. "Financial Interest" includes but is not necessarily limited to: salary, consulting fees, or other compensation for services that exceed $10,000 in any twelve (12) month period; serving as an officer/director; having an ownership interest in excess of 5% or $10,000 in a single entity; and intellectual property rights (patents, copyrights, and royalties from such rights). Appointment of relatives on a grant or contract constitutes a conflict of interest (see Sponsored policy C10). If a conflict exists, a memorandum (including a full explanation) addressed to the Vice Provost for Research must accompany this protocol submission. The study cannot go forward until the conflict is resolved or approved by the Vice Provost for Research.

PRINCIPAL INVESTIGATOR STATEMENT OF ASSURANCE:

- ❖ NO CHANGES IN THE PROTOCOL OR CONSENT FORM FOR THIS STUDY WILL BE IMPLEMENTED WITHOUT PRIOR APPROVAL BY THE IRB
- ❖ IT IS THE INVESTIGATORS' RESPONSIBILITY TO SUBMIT A TIMELY CONTINUING REPORT AS REQUESTED BY THE IRB.
- ❖ NOTIFY THE IRB WITHIN 10 WORKING DAYS, IN WRITING, OF ANY ADVERSE EVENTS IF THEY ARE: 1) UNEXPECTED (NOT MENTIONED IN THE CONSENT FORM), OR 2) SERIOUS AND/OR MORE SEVERE THAN ANTICIPATED (I.E. AS INDICATED ON THE INFORMED CONSENT FORM), OR 3) AT LEAST POSSIBLY RELATED TO STUDY DRUG OR STUDY PROCEDURES (IN THE PI'S JUDGMENT).
- ❖ REPORT ALL DEATHS REGARDLESS OF CASUALITY WITHIN 10 WORKING DAYS.
- ❖ NOTIFY THE IRB IMMEDIATELY UPON TERMINATION OF THIS STUDY AND/OR DEPARTURE OF THE PRINCIPAL INVESTIGATOR FROM THIS INSTITUTION OR CHANGE IN THE PRINCIPAL INVESTIGATOR FOR THIS STUDY.

SIGNATURES:

THE UNDERSIGNED AGREES TO FOLLOW AND ABIDE BY THE POLICIES AND PROCEDURES OF THE UNIVERSITY OF MIAMI FOR RESEARCH INVOLVING HUMAN PARTICIPANTS.

THE UNDERSIGNED IS (PLEASE CHECK ONE): ☒ A FULL-TIME UNIVERSITY OF MIAMI FACULTY MEMBER OR ☐ A FULL-TIME JMH/PUBLIC HEALTH TRUST EMPLOYEE, WHO ASSUMES RESPONSIBILITY FOR THIS STUDY.

Principal Investigator's Signature	LESLIE BAUMANN Print Name	7/14/03 Date
Division Chief's Signature	Print Name	Date
Departmental Chairman's Signature	William H Eaglstein Print Name	7/15/03 Date
Departmental Reviewer's Signature (If Applicable)	Print Name	Date

APPENDIX A

DATE: ____ ____ - ____ ____ - ____ ____ **STUDY PARTICIPANT NUMBER:** ____ ____

STUDY PARTICIPANT INITIALS: ____ ____ ____

Investigator Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of the study participant's face, how would you evaluate the:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Roughness of the skin to touch

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Other observations:

Changes in seborrheic keratoses:_____

Changes in pigmentation:_____

Changes in actinic keratoses:_____

APPENDIX B

DATE: ____ ____ - ____ ____ - ____ ____ **STUDY PARTICIPANT NUMBER:** ____ ____

STUDY PARTICIPANT INITIALS: ____ ____ ____

Study Participant Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of your face, how would you evaluate your:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Roughness of your skin to touch

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Comments: _____

_____

_____

_____

APPENDIX C

DATE: ____ ____ - ____ ____ - ____ ____ STUDY PARTICIPANT NUMBER: ____ ____

STUDY PARTICIPANT INITIALS: ____ ____ ____

Independent Dermatologist Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of the study participant's face, how would you evaluate the:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Other observations:

Changes in seborrheic keratoses:_____

Changes in pigmentation:_____

Changes in actinic keratoses:_____

APPENDIX D

DATE: ___ ___ - ___ ___ - ___ ___ STUDY PARTICIPANT NUMBER: ___ ___

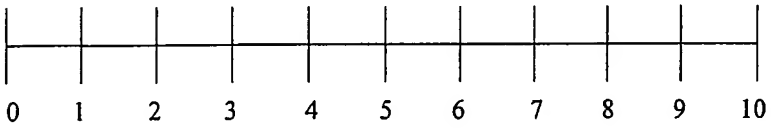
STUDY PARTICIPANT INITIALS: ___ ___ ___

Participant VAS Scales for Aldara™ Study

Day 0 and Week 16:

Overall, how do you rate the appearance of your skin?

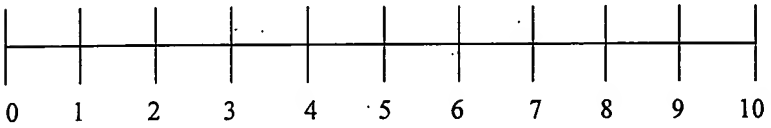
0= Not satisfied 10= Very satisfied



Week 16:

Overall, how do you rate any side effects related to using this cream?

0= Not tolerable 10= Tolerable



UNIVERSITY OF Miami
SCHOOL OF MEDICINE

UM COSMETIC CENTER
PARTICIPANT INSTRUCTION SHEET

Pilot Study of the Use of Aldara™ (imiquimod 5%) for the Treatment of Photoaging

A study doctor and a member of the research staff will initially demonstrate the amount of study medication to be applied. If you are applying the study medication after a shower or bath, you should wait 20 minutes before application. The study medication should be applied at least 10 minutes before going to be to minimize transfer of the cream to your bedding.

Apply the study medication every other day. If irritation develops, stop using the cream for 24 hours, apply moisturizer, and then resume use. If irritation continues, stop using the study medication and call the UM Cosmetic Center at 305-324-7546 to speak with a member of the research staff immediately. At your Week 2 visit, the study doctor will decide whether to increase application to once per day or decrease it to every third day.

In the morning:

1. Wash your face with cleanser.
2. Apply moisturizer.
3. Apply sunscreen.
4. Apply makeup as usual.

In the evening, before going to bed:

1. Wash your face with cleanser.
2. Apply a pea-sized amount (1 packet) of study medication using a clean, washed finger in a thin layer on your face, rubbing it in.
3. Apply moisturizer over study medication, if desired.
4. Wash your hands using a mild soap and water.
5. Leave cream on for 6-10 hours, and then wash off with mild soap and water in the morning.

Avoid touching your eyes, lips, mouth, nose, and any areas with cuts or scrapes, as the study medication may irritate these areas. If contact with any of these areas occurs, rinse thoroughly with water. Immediately following application, wash your hands using a mild soap and water.

REMINDERS

Avoid:

- showering, bathing or swimming for at least 3 hours after application of study medication
- long exposure to sunlight or other UV light
- scratching

For Follow-Up Visits:

- Notify research staff if you are running out of study medication packets.
- Return unused packets of study medication at your exit visit.

PROTOCOL

TITLE: Pilot Study of the Use of Aldara™ (imiquimod 5%) for the Treatment of Photoaging

Principal Investigator: Leslie S. Baumann, MD
Division of Cosmetic Dermatology, Department of Dermatology
University of Miami School of Medicine

1.0 BACKGROUND INFORMATION:

Aldara™ (Imiquimod topical 5%) is an FDA-approved topical therapy for the treatment of genital warts. Imiquimod topical 5% induces the production of several cytokines such as interferon, which is known to aid in the elimination of viral infections such as the one that causes by genital warts. These cytokines might also have an effect on photoaging.

It has been shown in case series that Aldara™ (imiquimod 5%) cream also plays a role in the elimination of skin cancers such as basal cell carcinomas through the induction of cytokines. While the anticarcinogenic effects are beyond the scope of this pilot study, it is important to determine whether this compound can be used for photoaging without major side effects. In our practice, we have used Aldara™ (imiquimod 5%) for the treatment of basal cell carcinomas and have noted an improvement of the surrounding photoaged skin.

Alternative treatments for photoaging include topical retinoids such as Retin-A®, Accutane®, and Tazorac®, and resurfacing treatments such as chemical peels and dermabrasion. However, retinoids can cause redness, flaking, and irritation of the skin, and cannot be tolerated by some patients. Skin resurfacing treatments involve injury to the epidermis. This study will assess the efficacy and safety of topical Aldara™ (imiquimod 5%) cream for the treatment of photodamaged skin.

2.0 STUDY OBJECTIVE:

The primary objectives of this study are to evaluate the safety and efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photodamaged skin.

3.0 CLINICAL HYPOTHESES

Aldara™ (imiquimod 5%) will have a beneficial effect on photodamaged skin.

Treatment with Aldara™ (imiquimod 5%) will have an acceptable safety profile when used topically for the treatment of photodamaged skin.

4.0 STUDY DESIGN

This study will be an open-label, pilot study to examine the safety and efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photoaging. There will be no randomization procedure for this study. Twenty participants will be enrolled. Participants will be assessed clinically two weeks prior to beginning treatment with the study medication (Week -2); participants who meet the study criteria will be asked to discontinue the use of all topical medications on the treatment sites for two weeks prior to using the study medication. Women will undergo a urine pregnancy test prior to receiving the study medication. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study. On Day 0, the study participants will be provided with enough packets of the study cream for 2 weeks of every other day application (1 packet = 1 application). At the Week 2 visit, participants will be assessed for tolerability of gel and usage will either stay the same, be increased to once daily application, or be decreased to every third day application. Further study medication will be distributed at this time. Participants will be asked to apply the study cream to the face and will be followed for a period of 16 weeks.

5.0 EVALUATION CRITERIA

5.1 Efficacy Measures

- Visioscan® Measurements (device that measures skin texture)
- Tewameter® Measurements (device that measures water loss from skin)
- Investigator Assessment
- Participant Assessment
- Blinded Independent Dermatologist Assessment
  - Serial color and ultraviolet photography of participants' faces

5.2 Safety Measures

- Number of adverse event incidents
- Frequency of incidents
- Severity of incidents

6.0 STUDY POPULATION

20 healthy volunteers with photodamaged skin.

7.0 INCLUSION/EXCLUSION CRITERIA

7.1 INCLUSION CRITERIA

- Healthy, male or female, participants between the ages of 18 and 70.
- Presence of photodamaged skin on the face, as assessed clinically by the investigator.
- Able to read and sign informed consent and photographic release.

- Willing and able to follow instructions, remain in the study for 18 weeks and complete follow-up visit schedule.
- Willing to discontinue the use of all topical medications on the treatment sites for two weeks prior to commencement of using study cream.
- Willing to undergo redness and inflammation in areas of precancerous and cancerous skin lesions during the course of the study.
- Female participants must have a negative pregnancy test upon enrollment, be non-lactating and using a consistent method of birth control without changes during the course of the study.

7.2 EXCLUSION CRITERIA

- Known allergy to study medication.
- Known allergy to adhesives.
- Unable to return for follow-up visits.
- Female study participants who are pregnant, breastfeeding, or planning a pregnancy during the course of the study.
- Have used topical retinoids (ex: Retin-A®, Renova®, Tazorac®) or oral retinoids (ex: Accutane®, Targretin®) in the 4 weeks before the study.
- Any uncontrolled systemic disease.
- History of cold sores around the mouth or on the lips.
- History of two or more basal cell carcinomas on the hands or face.
- Unable or unwilling to wear a sunscreen daily while participating in the study.
- Unwilling to limit ultraviolet light exposure.
- Participants concurrently receiving UVA, UVB, Narrowband UVB or PUVA therapies.
- Anticipated need for surgery or hospitalization during the study.
- Participation in another research trial in which treatment was received in the past 30 days.

8.0 MATERIALS

8.1 Study Medications

Aldara™ (imiquimod 5%) cream, supplied in 250mg single-use packets

8.2 Instructions for Use and Application

In the morning, participants will be instructed to wash the face with a gentle cleanser, apply moisturizer, apply sunscreen and, if used, apply makeup as usual. In the evening, participants will be instructed to wash the face with a gentle cleanser. Every other evening after washing, participants will apply a pea-sized amount (1 packet) of the study medication to the face, spreading it evenly over the surface. If desired, participants may apply moisturizer over the study medication. Participants will be instructed to wash their hands after application so they do not spread the cream in the mouth or eyes. If irritation develops, participant should stop using the study medication for a day and apply moisturizer. Participants will follow this every-other-day application schedule until the Week 2 visit. At the Week 2 visit, the investigator will determine any changes to the application schedule. If no irritation develops, participants may begin using the study

medication cream daily. If irritation continues, participants will be instructed to decrease the application of the cream to every third day and to contact the study site. The cleanser and moisturizers used will be approved by the study doctor to ensure that they do not contain any ingredients that may change the outcome of the study.

8.3 Frequency

For the first two weeks from Day 0 to Week 2 (Day 14), the study cream will be applied at an initial frequency of one time every other day. A small amount (1 packet, about the size of a pea) will be placed on the finger and evenly distributed on the face. After application the hands will be washed with a mild soap. At the Week 2 visit, participants who are not experiencing irritation will be instructed to increase the dosage to one time per day. Those that are experiencing irritation will either use the study cream every third day or will continue on an every other day regimen, as determined by the study doctor.

8.4 Other Study Supplies

- Mild soap
- Moisturizer
- Sunscreen
- Urine pregnancy tests
- Canfield facial camera, a fixed-position, standardized camera system
- Color and black and white (for measurement of regular UV damage) film
- Photographic paper
- Visioscan®
- Tewameter®

9.0 METHODS

9.1 Study Entry Procedures

Prospective subjects, as defined by the inclusion and exclusion criteria, will be considered for entry into this study. The study will be reviewed with the potential participant and informed consent will be obtained before any study-related procedures are conducted, including photographs.

Once enrolled, the study participants will be asked to discontinue the use of all topical medications to the treatment sites for two weeks prior to using the study medication. Women will undergo a urine pregnancy test. Women with a positive pregnancy test will be excluded. Female study participants will be required to use a reliable form of birth control during the course of the study. Acceptable forms of birth control include: abstinence from heterosexual intercourse, birth control pills, patch, or implant; depo-progesterone injections; barrier contraceptives such as a condom, diaphragm, and spermicidal foam or jelly (combination of at least two of these methods; intrauterine device (IUD); or surgical sterilization (hysterectomy or tubal ligation).

9.2 Study Visit Procedures

Participants who are enrolled in the study will return 2 weeks later for the Day 0 visit. Female participants will undergo a urine pregnancy test. Women with a positive pregnancy test at Day 0 will be discontinued from the study.

On Day 0, the study participants will be given enough packets of study cream for 2 weeks of every other day application (1 packet = 1 application). After review with the research team, the participants will also be provided with an instruction sheet detailing application procedures. At this visit, participants will be instructed to begin using the study medication every other day. The study participant and investigator will assess the safety and efficacy of the study medication using the procedures described below.

Follow-up evaluations will occur at visits on Week 2, Week 4, Week 8, Week 12, and Week 16. This schedule has been chosen in order to assess adverse events quickly and to have a monthly evaluation of treatment response. At the Week 2 visit, participants will be assessed for tolerability of the study medication and usage will either stay the same, be increased to once daily application, or be decreased to every third day application. Further study medication will be distributed at this time. At each follow-up visit, the study participant and investigator will assess the safety and efficacy of the study medication using the procedures described below. If the participants use more than the initial packets of study medication they were given, more packets will be dispensed as needed, and the number of packets they have been given will be recorded.

9.2.1 Procedures to occur

Efficacy

- **Visioscan® Measurements**

At each visit, Visioscan® measurements will be taken in order to determine the texture of the facial skin. The Visioscan® measures 4 parameters: smoothness, roughness, scaliness, and wrinkles. Using an eyebrow pencil, which is easy to wash off, a rectangle will be drawn on the participant's face to mark the site for camera placement. A circular sticker will be placed over the rectangle, the hand-held camera will be placed over the circle, and a close-up picture of the skin will be taken.

- **Tewameter® Measurements**

Tewameter® measurements will be taken at each visit in order to quantify water loss from facial skin. A double-sided sticking strip will be placed on the participant's skin at the measurement site. The probe will be affixed to the other side of the sticking strip. Measurements will be recorded for 30 seconds.

- **Investigator Assessment**

At each visit, the investigator will evaluate the facial skin using a questionnaire. The Investigator Questionnaire (Appendix A) will assess the appearance of a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) spider veins, and e) brown pigmentation on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe). Participants will also be clinically evaluated for the presence of other photoaging-related lesions, such as actinic keratoses. The number of these lesions will be counted.

- **Participant Assessment**

At each visit, participants will evaluate their facial skin using the same scale as the physician. The Participant Questionnaire (Appendix B) will also assess the appearance of a) fine wrinkles, b) coarse wrinkles, c) tactile roughness, d) spider

veins, and e) brown pigmentation on a 0-3 scale (0=none, 1=mild, 2=moderate, 3=severe). In addition, at Day 0 and Week 16, participants will complete visual analog scales (VAS) assessing the cosmetic appearance of the treated sites (Appendix D).

- **Serial Color Photography/Blinded Independent Dermatologist Assessment**

At each visit, the study participants will have color and ultraviolet photographs taken of their face (Canfield facial camera). At the end of the study, the photographs will be evaluated by a blinded independent dermatologist, comparing the study participants' photographs with their baseline photographs to assess the efficacy of the study medication. The Independent Dermatologist Questionnaire will employ the same assessment scale as that used by the investigator (Appendix C), except that the tactile roughness assessments will be eliminated.

Safety

At each visit study participants will be asked if they have experienced any adverse events that may have developed since starting the study medication (number, frequency and severity will be recorded), changes in their medications, and changes in any procedures. At the Week 16 visit, participants will complete a VAS scale (Appendix D) to assess the adverse events associated with treatment.

9.3 Schedule of Visits and Procedures

	Day -14	Day 0	Weeks 2, 4, 8, 12	Week 16
Informed Consent	X			
Participant Demographics	X			
Medical History, Allergies	X			
Concurrent Medications, Procedures	X	X	X	X
Adverse Events		X	X	X
Pregnancy Test (Urine)	X	X		
Participant Assessment		X	X	X
Participant VAS Assessment		X		X
Facial Photography		X	X	X
Visioscan® Measurements		X	X	X
Tewameter® Measurements		X	X	X
Investigator Assessment		X	X	X
Medication Review, Dispense		X	X	
Medication Collection				X

9.4 Study Exit

Participation will be considered completed after use of the cream for 16 weeks.

10.0 STATISTICAL PROCEDURES

10.1 Demographics

Descriptive statistical methods will be used to describe the demographic (age, gender, race/ethnicity) composition of the study population.

10.2 Visioscan® and Tewameter® Measurements

At each visit, Visioscan® measurements will be taken to assess skin texture and Tewameter® measurements will be taken to assess water loss from skin. These measurements over the course of the study will be analyzed using Friedman and Wilcoxon signed rank tests, and pre- treatment (Week 0) and post-treatment (Week 16) measurements will be compared using the Friedman test.

10.3 Investigator Assessment

Investigator will complete the Investigator Questionnaire (Appendix A) at Day 0 and Weeks 2, 4, 8, 12, and 16. Treatment response over the course of the study will be analyzed using Friedman and Wilcoxon signed rank tests, and pre-treatment (Week 0) and post-treatment (Week 16) responses for each efficacy variable will be compared using the Friedman test.

10.4 Serial Color Photography/Blinded Independent Dermatologist Assessment

Blinded independent dermatologist will complete a questionnaire (Appendix C) based on the photographs from Day 0 and Weeks 2, 4, 8, 12, and 16. Treatment response over the course of the study will be analyzed using Friedman and Wilcoxon signed rank tests, and pre-treatment (Week 0) and post-treatment (Week 16) responses for each efficacy variable will be compared using the Friedman test.

10.5 Participant Assessment

Participants will complete the Study Participant Questionnaire (Appendix B) at Day 0 and Weeks 2, 4, 8, 12, and 16. Treatment response over the course of the study will be analyzed using Friedman and Wilcoxon signed rank tests, and pre-treatment (Week 0) and post-treatment (Week 16) responses for each efficacy variable will be compared using the Friedman test. Additionally, at the Day 0 and Week 16 visits, participants will complete VAS scales assessing overall satisfaction with the treatment (Appendix D). This data will be analyzed using the Friedman test.

10.6 Physician vs. Independent Observer Assessment

For each visit (Day 0 and Weeks 2, 4, 8, 12, and 16) investigator and blinded independent dermatologist assessments will be compared using Pearson correlation coefficients.

10.7 Adverse Events

The frequency, severity and duration of adverse events will be condensed and summarized using descriptive statistical methods. In addition, at the exit visits, participants will fill out a VAS scale rating the side effects of treatment with the cream (Appendix D); this data will be analyzed using descriptive statistical methods.

11.0 VISIT SCHEDULE/LOG

11.1 Day -14 (two weeks prior to beginning application of study medication)

- Informed consent will be obtained.
- Study participant demographic information will be obtained.
- Medical history, concurrent medication, and allergy history will be obtained.
- Study participant will be asked to discontinue the use of all topical medications to the affected areas for two weeks prior to starting study medication.
- Female participants will undergo a urine pregnancy test. If negative, participant will be enrolled in the study. If positive, participant will be excluded from study.
- Participants will be instructed to return in two weeks.

11.2 Day 0

- Females will undergo a urine pregnancy test. If negative, participant will commence using study medication. If positive, participant will be exited from study.
- Participant questionnaire will be completed.
- VAS scale completed by participant to assess skin appearance.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® measurement to assess skin texture.
- Tewameter® measurement to assess water loss from skin.
- Investigator questionnaire will be completed.
- Enough packets of study medication for 2 weeks of every-other-day application will be given to each study participant and recorded, and instructions on use given.

11.3 Week 2

- Completion of study participant questionnaire.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.
- Study doctor will assess adverse events from study medication and determine whether the participant will increase study medication use to every day, decrease it to every third day, or continue using the medication every other day. Additional packets of study cream will be given to participants in appropriate amounts, and the number of packets will be recorded.

11.4 Weeks 4, 8, and 12

- Completion of study participant questionnaire.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.

- Amount of study medication used will be reviewed with participant and, if needed, additional packets of study cream will be given to participants. The number of packets distributed will be recorded.

11.5 Week 16 (Exit Visit)

- Completion of study participant questionnaire.
- VAS scale completed by participant to assess skin appearance.
- VAS scale completed by participant to assess adverse events related to treatment.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.
- Unused medication packets will be collected.

12.0 COMPLIANCE

Participants will also be asked to return to the clinic for follow-up visits. At each visit, usage of study medication will be reviewed with participants to ensure that they are using the correct amount. The total number of study medication packets given to each participant will be recorded on a medication log, and participants will be asked to return all unused packets at the exit visit.

13.0 SAFETY ASSESSMENTS

The safety of Aldara™ (imiquimod 5%) cream will be assessed by evaluation of the frequency, severity and duration of adverse events. Throughout the course of the study, all adverse events will be monitored and reported on an adverse event report form, which includes seriousness, severity, action taken, and relationship to study drug. If an adverse event occurs, the first concern will be the safety of the study participant.

The severity assessment of an AE will be completed using the following definitions as guidelines:

mild	awareness of signs or symptoms, but easily tolerated
moderate	discomfort enough to cause annoyance
moderately severe	discomfort enough to cause interference with usual activity
severe	incapacitating with inability to work or do usual activity

Relationship to study drug

A determination of the relationship between an adverse event and the study drug will be considered to be present if a determination is made that there is a reasonable possibility that the adverse event may have been caused by the drug. This assessment will be

completed using the following definitions: Related, Probably Related, Possibly Related, Unlikely to Be Related, Not Related.

At the end of study medication use, the safety of Aldara™ (imiquimod 5%) will be determined by:

a) reports of any adverse events during the course of the study
b) evaluation of post-treatment participant Visual Analog Scale (VAS) responses assessing adverse events

14.0 EFFICACY ASSESSMENTS

This study will evaluate the efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photoaging.

At the end of study medication use, the efficacy of Aldara™ (imiquimod 5%) will be determined by:

a) serial photography evaluated by blinded independent dermatologist
b) comparison of serial physician questionnaire responses over the course of treatment
c) comparison of serial study participant questionnaire responses over the course of treatment
d) comparison of pre- and post-treatment Visual Analog Scale (VAS) responses assessing skin appearance

15.0 PARTICIPANT DISCONTINUATION

The Investigator may discontinue individual study participants from the study at any time. Study participants will be encouraged to complete the study; however, they may voluntarily withdraw at any time from the study. The Investigator will provide a written report on the reason for discontinuation. If a study participant withdraws or is discontinued from the study before completion, every effort should be made to complete the scheduled visits.

A study participant may be removed from the study for the following medical or administrative reasons:

15.1 Adverse event

If a participant suffers an AE that, in the judgment of the Investigator, presents an unacceptable consequence or risk to the participant, the participant may be discontinued from further participation in the study.

15.2 Intercurrent illness

A study participant may also be discontinued from the study if, in the judgment of the Investigator, he or she develops an intercurrent illness or complication that is not consistent with the protocol requirements.

15.3 Administrative Discontinuation

A participant may be discontinued from the study for the following reasons:

Failure to return for follow-up visits

Reasonable efforts will be made to monitor the participants for compliance.

16.0 PROCEDURES IN CASE OF AN EMERGENCY

Each study participant will be given information regarding emergency contacts. This information will contain numbers for the research staff and the doctor.

17.0 PARTICIPANT INFORMATION

All information pertaining to each study participant will be kept confidential. The records will be kept in the files of the Principal Investigator conducting this study at the UM Cosmetic Center located in the Cedars Medical Center, 1295 N.W. 14th Street, Suite K, Miami, FL. The records will be locked when not in use. The charts will be coded by study participant number and initials on the exterior of the study binders.

18.0 ETHICAL APPROVAL

The University of Miami Institutional Review Board will review the study protocol, including study participant information and consent form. The study will not commence until full approval is received by the IRB.

APPENDIX A

DATE: ___ ___ - ___ ___ - ___ ___ STUDY PARTICIPANT NUMBER: ___ ___

STUDY PARTICIPANT INITIALS: ___ ___ ___

Investigator Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of the study participant's face, how would you evaluate the:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Roughness of the skin to touch

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Other observations:

Changes in seborrheic keratoses:_____

Changes in pigmentation:_____

Changes in actinic keratoses:_____

APPENDIX B

DATE: ____ ____ - ____ ____ - ____ ____ STUDY PARTICIPANT NUMBER: ____ ____

STUDY PARTICIPANT INITIALS: ____ ____ ____

Study Participant Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of your face, how would you evaluate your:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Roughness of your skin to touch

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Comments: _____

_____

_____

_____

APPENDIX C

DATE: ___ ___ - ___ ___ - ___ ___ STUDY PARTICIPANT NUMBER: ___ ___

STUDY PARTICIPANT INITIALS: ___ ___ ___

Independent Dermatologist Questionnaire for Aldara™ Study

Circle one:

Day 0 Week 2 Week 4 Week 8 Week 12 Week 16

Concerning the appearance of the study participant's face, how would you evaluate the:

Fine wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Coarse wrinkles

0 = None 1 = Mild 2 = Moderate 3 = Severe

Spider veins

0 = None 1 = Mild 2 = Moderate 3 = Severe

Brown pigmentation

0 = None 1 = Mild 2 = Moderate 3 = Severe

Other observations:

Changes in seborrheic keratoses:_____

Changes in pigmentation:_____

Changes in actinic keratoses:_____

APPENDIX D

DATE: ____ ____ - ____ ____ - ____ ____ STUDY PARTICIPANT NUMBER: ____ ____

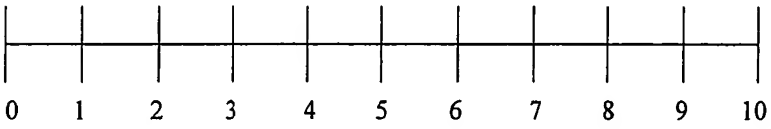
STUDY PARTICIPANT INITIALS: ____ ____ ____

Participant VAS Scales for Aldara™ Study

Day 0 and Week 16:

Overall, how do you rate the appearance of your skin?

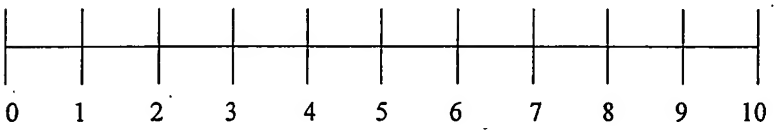
0= Not satisfied 10= Very satisfied



Week 16:

Overall, how do you rate any side effects related to using this cream?

0= Not tolerable 10= Tolerable



UNIVERSITY OF Miami
SCHOOL OF MEDICINE

UM COSMETIC CENTER
PARTICIPANT INSTRUCTION SHEET
Pilot Study of the Use of Aldara™ (imiquimod 5%) for the Treatment of Photoaging

A study doctor and a member of the research staff will initially demonstrate the amount of study medication to be applied. If you are applying the study medication after a shower or bath, you should wait 20 minutes before application. The study medication should be applied at least 10 minutes before going to be to minimize transfer of the cream to your bedding.

Apply the study medication every other day. If irritation develops, stop using the cream for 24 hours, apply moisturizer, and then resume use. If irritation continues, stop using the study medication and call the UM Cosmetic Center at 305-324-7546 to speak with a member of the research staff immediately. At your Week 2 visit, the study doctor will decide whether to increase application to once per day or decrease it to every third day.

In the morning:

1. Wash your face with cleanser.
2. Apply moisturizer.
3. Apply sunscreen.
4. Apply makeup as usual.

In the evening, before going to bed:

1. Wash your face with cleanser.
2. Apply a pea-sized amount (1 packet) of study medication using a clean, washed finger in a thin layer on your face, rubbing it in.
3. Apply moisturizer over study medication, if desired.
4. Wash your hands using a mild soap and water.
5. Leave cream on for 6-10 hours, and then wash off with mild soap and water in the morning.

Avoid touching your eyes, lips, mouth, nose, and any areas with cuts or scrapes, as the study medication may irritate these areas. If contact with any of these areas occurs, rinse thoroughly with water. Immediately following application, wash your hands using a mild soap and water.

REMINDERS

Avoid:

- showering, bathing or swimming for at least 3 hours after application of study medication
- long exposure to sunlight or other UV light
- scratching

For Follow-Up Visits:

- Notify research staff if you are running out of study medication packets.
- Return unused packets of study medication at your exit visit.

INFORMED CONSENT

Pilot Study of the Use of Aldara™ (imiquimod 5%) Cream for the Treatment of Photoaging

Study Participant Identification number: _____

INTRODUCTION

You are being asked to voluntarily participate in a clinical research study to evaluate a topical cream for photoaging (sun-damaged skin). This consent form describes the study and your role in it. You are to read this form carefully and ask any questions you have regarding the information it contains. This consent form may contain words that you do not understand. Please ask the study doctors or the research staff to explain any words or information that you do not fully understand. You will be given a signed and dated copy of this consent form for your own information.

PURPOSE OF STUDY

Aldara™ (imiquimod topical 5%) cream is an FDA-approved topical therapy for the treatment of genital warts (caused by the human papilloma virus). Imiquimod topical 5% stimulates the production of several cytokines (substances) in the body; these cytokines are thought to make the skin stronger to attack the virus. It is possible that these cytokines might also have an effect on photoaging.

Case studies have shown that Aldara™ (imiquimod 5%) cream also plays a role in the elimination of skin cancers such as basal cell carcinomas through the stimulation of cytokines. While the anticarcinogenic (cancer-fighting) effects are beyond the scope of this pilot study, it is important to determine whether this compound can be used for photoaging without major side effects. Aldara™ (imiquimod 5%) has been used for the treatment of basal cell carcinomas, and improvement of the surrounding photoaged skin has been noted. For the purposes of this study, Aldara™ (imiquimod 5%) cream is being used as an investigational drug. It is not FDA-approved in the United States for the treatment of photoaging. That is why this study is being conducted. The objectives of this study are to evaluate the safety and efficacy of Aldara™ (imiquimod 5%) cream for the treatment of photodamaged skin.

This study is an eighteen week, open-label research study to evaluate the efficacy and safety of a topical treatment product for photoaging in participants between the ages of 18 and 70. You will use the study medication on your full face. In addition, you will be given a gentle cleanser, moisturizer, and sunscreen. All supplies will be provided by study doctors. This study will require 7 visits to the Center over an 18-week period. Approximately 20 participants will participate in this study at this office.

In order to be eligible for enrollment into the study you must:

- Be able to read and sign informed consent and photographic release.
- Be a healthy, male or female, participant between the ages of 18 and 70.
- Have photodamaged skin on the face, as assessed clinically by the investigator.

- Be willing and able to follow instructions, remain in the study for 18 weeks and complete follow-up visit schedule.
- Be willing to discontinue the use of all topical medications on the treatment sites for two weeks prior to commencement of using study cream.
- Be willing to undergo redness and inflammation in areas of precancerous and cancerous skin lesions during the course of the study.
- Female participants must have a negative pregnancy test upon enrollment, be non-lactating and using a consistent method of birth control without changes during the course of the study.

You are <u>not</u> eligible for enrollment into this study if you:

- Are younger than 18 years of age or older than 70 years of age.
- Have a known allergy to study medication.
- Have a known allergy to adhesives.
- Are unable to return for follow-up visits.
- Are a female study participant who is pregnant, breastfeeding, or planning a pregnancy during the course of the study.
- Have used topical retinoids (ex: Retin-A®, Renova®, Tazorac®) or oral retinoids (ex: Accutane®, Targretin®) in the 4 weeks before the study.
- Have any uncontrolled systemic disease.
- Have a history of cold sores around the mouth or on the lips.
- Have a history of two or more basal cell carcinomas on the hands or face.
- Are unable or unwilling to wear a sunscreen daily while participating in the study.
- Are unwilling to limit ultraviolet light exposure.
- Are concurrently receiving UVA, UVB, Narrowband UVB or PUVA therapies.
- Have an anticipated need for surgery or hospitalization during the study.
- Have participated in another research trial in which treatment was received in the past 30 days.

STUDY PROCEDURES

During your first visit to the office, the study will be reviewed with you, and you will be asked to sign this informed consent form and photography consent form if you agree to participate. Your face will be examined by one of the study doctors to see if you are eligible to participate in the study. You will be assessed to ensure that you meet all of the inclusion and none of the exclusion criteria. Visioscan® (device that measures skin texture) measurements, Tewameter® (device that measures water loss from skin) measurements, and photographs will be taken at appropriate visits, as described below. You will be asked to fill out evaluation forms regarding your photodamaged skin as described below.

If you qualify and agree to participate in the study, you will be given the study medication at the second visit. For the first two weeks, you will apply the study medication to your face every other evening according to the participant instruction sheet. All participants will be provided with sunscreen, face wash, and moisturizer to use during the course of the treatment. After using the study medication for 2 weeks, you will return for an office visit, and the study doctor will decide whether you should continue to apply the study cream every other day, increase

application to every day, or decrease it to every third day. Following is the list of visits and the events which will occur at each visit.

Day -14 (two weeks prior to beginning application of study medication)

- Informed consent will be obtained.
- Your demographic information will be obtained.
- Your medical history, concurrent medication, and allergy history will be obtained.
- You will be asked to discontinue the use of all topical medications to the affected areas for two weeks prior to starting study medication.
- Female participants will undergo a urine pregnancy test. If negative, you will be enrolled in the study. If positive, you will be excluded from study.
- You will be instructed to return in two weeks.

If successfully enrolled, you will be instructed to discontinue all topical medications on your face and return in 2 weeks. You may continue to use your normal lipstick and/or eye makeup during the study (if applicable).

Day 0

- Females will undergo a urine pregnancy test. If negative, you will commence using study medication. If positive, you will be exited from study.
- You will complete a study participant questionnaire.
- You will complete a VAS scale to assess skin appearance.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® measurement to assess skin texture.
- Tewameter® measurement to assess water loss from skin.
- Investigator questionnaire will be completed.
- Enough packets of study medication for 2 weeks of every-other-day application will be given to you and recorded, and instructions on use given.

Week 2

- You will complete a study participant questionnaire.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.
- Study doctor will assess adverse events from study medication and determine whether you will increase study medication use to every day, decrease it to every third day, or continue using the medication every other day. Additional packets of study cream will be given to you in appropriate amounts, and the number of packets will be recorded.

Weeks 4, 8, and 12

- You will complete a study participant questionnaire.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.

- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.
- Amount of study medication used will be reviewed with you and, if needed, additional packets of study cream will be given to you. The number of packets distributed will be recorded.

Week 16 (Exit Visit)

- You will complete a study participant questionnaire.
- You will complete a VAS scale to assess skin appearance.
- You will complete a VAS scale to assess adverse events related to treatment.
- Study personnel will review any adverse events, changes in concurrent medications, or changes in concurrent procedures.
- Color and ultraviolet facial photographs will be taken.
- Visioscan® and Tewameter® measurements will be taken.
- Investigator questionnaire will be completed.
- Unused medication packets will be collected.

RISKS

All medications have side effects and these can sometimes be unforeseen. In this study, Aldara™ (imiquimod 5%) is an investigational treatment for the improvement of photoaging, and all of its possible side effects are not known. In previous studies, enrolled participants reported some side effects which you may experience.

	Application Site	Remote Site	Systemic (Whole Body)
Likely (Happens to 20 – 60%)	Erythema (redness), erosion (skin loss), excoriation (scraping)/ flaking, itching		
Occasional (Happens to 5 – 20%)	Edema (swelling), induration (hardness), ulceration (deeper skin loss), scabbing, burning, pain, fungal infection		Headache
Rare (Happens to < 5%)	Vesicles (tiny blisters), soreness, hypopigmentation (light spots), hyperpigmentation (dark spots), irritation, rash, sensitivity, stinging, tenderness	Erythema, ulceration, edema, erosion, induration, excoriation/flaking, bleeding, burning, itching, pain, tenderness, tinea cruris (a fungal infection)	Influenza-like symptoms, myalgia (muscle aches), fatigue, fever, diarrhea

Follow-up information on the hypopigmentation (light spots) and hyperpigmentation (dark spots) experienced by previous study participants suggests that these skin color changes may be permanent.

In addition, if you have precancerous lesions or skin cancers on your face, you will experience redness and possible erosions in the areas of those cancerous lesions. These effects have been seen in studies for Aldara™ (imiquimod 5%) for the treatment of skin cancer. The redness and erosions resolve when you stop using the study medication, but continued use of the study medication may result in elimination of the precancerous lesions or cancer. You should continue to use the study medication unless you feel that the redness and erosions are not tolerable.

Participants with sensitivity to adhesives may experience a localized skin reaction to the adhesive strips used for Visioscan® and Tewameter® measurements.

The study medication must be used only by you and should be kept out of the reach of children or others of limited capacity to read or understand.

Imiquimod topical 5% cream is not recommended for use by patients with a known hypersensitivity to it or to any of the ingredients of the product. The photosensitivity of the product is unknown, so you should minimize the exposure of treated areas to sunlight and sunlamps. You should also use the provided sunscreen while using the study medication. Although Aldara™ (imiquimod 5%) has not been associated with birth defects, fetal harm is unlikely but possible. This medication has been shown to have minimal systemic absorption. No interference with laboratory tests has been observed. Beneficial effects from the study cream are possible after discontinuation of cream use, but it is unknown.

Women: In addition, if you are pregnant or become pregnant, there may be a risk of spontaneous abortion or fetal malformation. You must not enter the study if you are breast-feeding a baby or if you intend to try to become pregnant. The effects of imiquimod on an unborn baby have not been studied and are unknown. The risk that it could cause a miscarriage or affect the baby's development is not known. You will not be allowed to enter the study or to receive the study treatments if your pregnancy test is positive. You must use adequate contraceptive precautions during the study. Acceptable forms of birth control for this study include (1) use of oral contraceptives for at least 1 month prior to treatment and for the duration of the study, OR (2) the use of two forms of contraception (i.e. condoms plus spermacide), (3) be surgically sterile or post-menopausal for at least 1 year, OR (4) abstinence from heterosexual sex. <u>If you have any suspicion that you are pregnant, or should you become pregnant during the course of this study, you must inform Dr. Baumann immediately.</u>

If you experience any illness or discomfort during the study, you should notify one of the study doctors. One of the study doctors will then evaluate you to determine if you should continue in the study.

Your participation in this medical research study may involve risks from the medications that are currently unforeseeable or unknown.

BENEFITS
By participating in this study, you may or may not receive any direct medical benefits, and improvement of your photoaging cannot be guaranteed. If you do receive benefit from the study medication and your photoaged skin improves cosmetically, these beneficial effects may be temporary.

ALTERNATIVE TREATMENTS
You do not have to participate in this study in order to be treated for your condition. The study doctors will discuss with you the advantages and disadvantages of these alternative treatments. Alternative treatments which are available for photoaging include:

- Topical retinoids (Altinac®, Renova®, Retin-A®, Accutane®, Tazorac®)
- Skin resurfacing (dermabrasion, chemical peels)

PAYMENT FOR PARTICIPATION
You will not receive payment for your participation in this study.

COSTS
You will be responsible for opportunity costs related with your participation in this study, such as parking and transportation.

COMPENSATION FOR INJURY
You may be exposed to risk of injury from participation in this study. If injury should occur, treatment in most cases will be available. If you have insurance, your insurance company may or may not pay for these costs. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay. Funds to compensate for pain, expenses, lost wages, or other damages caused by injury are not routinely available.

CONFIDENTIALITY
By signing this consent, you authorize the investigators and their staff to access your medical records and associated information as may be necessary for the purposes of this study. This information may also be shared with the manufacturer of the study medication, 3M Pharmaceuticals. Your records and results will not be identified as pertaining to you in any publication without your expressed permission. The investigators and their collaborators, staff, and the manufacturer of the study medication will consider your records confidential to the extent permitted by law. The Food and Drug Administration (FDA) and Department of Health and Human Services (DHHS) may review these research records. Your records may also be reviewed for audit purposes by authorized University of Miami employees or other agents who will be bound by the same provisions of confidentiality.

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which Aldara™ (imiquimod 5%) may ultimately be marketed, but your name will not be disclosed in these documents. Your name may be disclosed to the manufacturer of the study medication, 3M Pharmaceuticals, their agents, the governing health authorities, or the FDA (Food and Drug Administration), if they inspect your medical records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

The results of this research study may be presented at meetings or in publications; however, your identity will not be disclosed in such presentations.

In order to verify information collected in this study and to verify how the study is conducted, your medical records related to the study, this signed consent form, and any other regulatory documents associated with the study, may be inspected by the FDA, Department of Health and Human Services (DHHS) agencies, representatives of the manufacturer of the study medication, 3M Pharmaceuticals, governmental agencies in other countries, and by other regulatory agencies. By signing this form, you will authorize this access to your records. However, because of the need to release information to these parties, absolute confidentiality cannot be guaranteed.

RIGHT TO WITHDRAW

You understand that participation in this study is voluntary and that you are free to refuse to participate in this study or withdraw at any time. Your decision to discontinue participation at any time will not adversely affect your subsequent care at this institution or cause a loss of benefits to which you might be otherwise entitled; you are free to seek care from a health care provider of your choice at any time. Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you are a student, your desire not to participate, or your request to withdraw from the study, will not affect your grades or other academic standings within the University.

If you are an employee of the University, your decision to participate in or to withdraw from the study will not affect your employment within the University.

Additionally, your participation in the study may be ended by the study doctors or the sponsor without your permission at any time.

If any significant new findings about the study cream are learned during the course of the study that may change your decision to continue participation in the study, this information will be made available to you. One of the study doctors or the research staff will answer any questions that you may have regarding this investigation or your participation in the study.

If you have any research related questions or side effects during the study please contact Dr. Leslie Baumann at her office at 305-324-7546. Please call right away if you have an injury, illness or side effect. If you need to speak with her after hours, the recorder at the office will provide you with an alternate number. If you have any questions about your rights as a research subject, you may contact Ms. Maria Arnold, IRB Director, University of Miami, at 305-243-3195.

CONSENT

Pilot Study of the Use of Aldara™ (imiquimod 5%) Cream for the Treatment of Photoaging

I have read and understand the above information describing the medical research study in this consent form. A study doctor or the research staff have explained this information and answered all of my questions to my satisfaction. I voluntarily agree to participate in this research study.

I fully understand that use of the study medication (Aldara™, imiquimod 5%) in humans is limited, that safety and effectiveness of the study medication have not yet been fully established and that there is a risk of adverse (bad or harmful) reaction to the study cream. I understand that the study medication should only by used by myself and should be kept out of the reach of children or others of limited capacity to read or understand. I agree to abide by any participant instructions, reminders and precautions given to me before and during the study.

I understand that I will be given a signed and dated copy of this consent form.

By signing this form I authorize the release of my medical records and all other relevant study materials to the FDA, DHHS agencies, and governmental agencies in other countries and authorized University of Miami officials.

_____
Printed Name of Participant

_____ Date_____
Signature of Participant

_____
Printed Name of Person Explaining Consent

_____ Date_____
Signature of Person Explaining Consent

Principal Investigator: Leslie Baumann, MD

_____ Date _____
Signature of Principal Investigator

AUTHORIZATION FOR PHOTOGRAPHY OR TAPING IN A RESEARCH STUDY

Pilot Study of the Use of Aldara™ (imiquimod 5%) Cream for the Treatment of Photoaging

I hereby authorize the University of Miami, Department of Dermatology, Division of Cosmetic Dermatology, to take still photographs, videotapes and or sound recording of me.

I authorize the University to use in any manner said photographs, film, video or tape recordings, in whole or in part:

[ ] for any purpose whatsoever, including without limitation, all broadcast, promotional and advertising uses, and other commercial purposes;

[ ] for the purpose of teaching, research, scientific meetings and scientific publications, including professional journals or medical books.

I agree that the University of Miami, its Trustees, officers, employees, faculty and agents will not be responsible for any claims arising in any way out of the taking and use as described above of such photographs, and/or recordings. I understand that I will not have an opportunity to inspect and approve such photographs or recordings prior to their use.

_____	_____
Printed Name of Study Participant	Printed Name of Witness
_____	_____
Signature of Participant	Signature of Witness
_____	_____
Date	Date

IRB Protocol Number:_____

HIPAA Research Authorization Template – Form B
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit *the* ☑ *University of Miami* ☐ *Jackson Health System* ☐ *both*, and any of my doctors or other health care providers (together "Providers"), Principal Investigator and [*his /her/their/its*] collaborators and staff (together "Researchers"), to obtain, use and disclose health information about me as described below.

1. **The health information that may be used and disclosed includes:**
all information collected during the research and procedures described in the Informed Consent Form for the

   - ("the Research"); and
   - health information in my medical records that is relevant to the Research, includes my past medical history including medical information from my primary care physician and other medical information relating to my participation in the study.

2. **The Providers may disclose health information in my medical records to:**
   - the Researchers;
   - representatives of government agencies, review boards, and other persons who watch over the safety, effectiveness, and conduct of research; and
   - the sponsor of the Research, none (Print Sponsor Name),

   and its agents and contractors (together "Sponsor").

3. **The Researchers may use and share my health information:**
   - among themselves, with the Sponsor, and with other participating Researchers to conduct the Research; and
   - as permitted by the Informed Consent Form.

4. The Sponsor may use and share my health information for purposes of the Research and as permitted by the Informed Consent Form.

5. **Once my health information has been disclosed to a third party,** federal privacy laws may no longer protect it from further disclosure.

IRB Protocol Number:_____

6. **Please note that:**
   - You do not have to sign this Authorization, but if you do not, you may not participate in the Research. If you do not sign this authorization, your right to other medical treatment will not be affected.

You may change your mind and revoke (take back) this Authorization at any time and for any reason. To revoke this Authorization, you must write to:

Research Study Personnel Name: Leslie Baumann, MD
Address: 1295 NW 14th St., South Bldg, Suite K, Miami, FL 33125
Tel. No.: 305-324-7546

- However, if you revoke this Authorization, you will not be allowed to continue taking part in the Research. Also, even if you revoke this Authorization, the Providers, Researchers and the Sponsor may continue to use and disclose the information they have already collected to protect the integrity of the research or as permitted by the Informed Consent Form.
- While the Research is in progress, you may not be allowed to see your health information that is created or collected by *the ☑ University of Miami ☐ Jackson Health System ☐ both*, in the course of the Research. After the Research is finished, however, you may see this information as described in *the ☑ University of Miami ☐ Jackson Health System ☐ both*, Notice of Privacy Practices.

7. **This Authorization does not have an expiration (ending) date.**

8. **You will be given a copy of this Authorization after you have signed it.**

_____ Signature of participant or participant's legal representative

_____ Date

_____ Printed name of participant

_____ Printed name of legal representative (if applicable)

_____ Representative's relationship to participant

*** Copies with signature must be sent to: University of Miami Privacy Office. For questions contact the Human Subjects Research Office at 305-243-3197.**

Eggert STOCKFLETH
Claas ULRICH
Axel HAUSCHILD
Stephan LISCHNER
Thomas MEYER
Enno CHRISTOPHERS

Successful treatment of basal cell carcinomas in a nevoid basal cell carcinoma syndrome with topical 5% imiquimod

E. Stockfleth, C. Ulrich: Department of Dermatology of the Charité, Humboldt University, Schumannstraße 20/21, 10117 Berlin, Germany.
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Gorlin-Goltz syndrome, also referred to as naevoid basal cell carcinoma syndrome (NBCCS), is an autosomal dominant skin disease with complete penetrance and inconstancy of the four major findings: multiple naevoid basal cell carcinomas (BCCs), pits on palms and soles, skeletal abnormalities (for example, jaw cysts), and ectopic calcification. The treatment of multiple BCCs is still a matter of debate. We report three cases of multiple BCCs in Gorlin-Goltz syndrome treated with topical 5% imiquimod cream, an immune response modifier. Patients were successfully cleared of BCCs after treatment for 6-8 weeks. Histologically no apparent signs of BCC-persistence could be detected and no recurrences were detected during the 12 month follow up period. *(Key words: Gorlin-Goltz syndrome, basal cell carcinoma, immune response modifier, imiquimod.)*

The naevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin-Goltz syndrome, is an inherited dermatologic disease with an autosomal dominant pattern showing complete penetrance but extremely variable expressivity. The principal features of this syndrome vary and may include early appearing naevoid basal cell carcinomas (BCCs), palmar and plantar pits, multiple skeletal abnormalities, for example flattened facies, broad nasal root, mandibular prognathia, jaw cysts, intracranial calcification of falx cerebri and other structures, and anomalies of the ocular system, for example hypertelorism, cataract or strabismus [1-7]. A major complication of the disease is the enormous number of BCC lesions and their high risk of invasion of deep structures, especially when located in sun exposed skin areas such as the head and neck [1]. Lesions sometimes occur before 10 years of age.

Several factors play a role in the aetiology of this disease. Previous investigations of BCCs in NBCCS have shown an influence of the p53 tumor suppressor gene in the aetiology and pathogenesis of this disorder [8, 9]. However, the genetic mutations responsible for inducing NBCCS have been localized to gene locus 9 (9q22.3-q31) of the human PTC gene (PTCH). Two independent sequence changes in this human homolog of the drosophila patched gene (PTC) have been reported. The causative gene may function as a tumor suppressor [10-13]. Similar gene changes concerning PTCH and the human homologue of smoothened (SMOH) may contribute to the aetiology of BCCs in general [14, 15].

The definitive treatment for multiple BCCs in Gorlin-Goltz syndrome is still a matter of debate. A multiple-modality treatment including cryotherapy and reconstructive surgery is reported [16], with patients quite often showing a history of multiple operations. Radiation treatment is considered to be obsolete [10].

Imiquimod [1-(2-methylpropyl)-1H-imidazo(4,5-c)-quinoline-4-amine] is a topical immune response modifier, which has demonstrated both antiviral and anti-tumor activity in animal models [17, 18]. It is currently approved for the treatment of external genital warts and has been used successfully in the treatment of stucco keratoses [19]. This topically applied treatment stimulates production of pro-inflammatory cytokines locally, and enhances cell-mediated cytologic activity against viral targets [20]. Imiquimod 5% cream has also been used successfully in the treatment of BCCs [21]. In this paper we report the results of treatment of multiple BCCs with imiquimod 5% cream in three patients with inherited NBCCS.

Materials and methods and case reports

Three patients with NBCCS were clinically examined for the presence of BCCs and other NBCCS-related features, for example palmar and plantar pits, skeletal abnormalities and anomalies of the ocular system. All patients were seen by the same consultant who took a detailed history. Medical records of the patients were reviewed, including previous treatment and present medication. We report three cases of NBCCS, two women and one man, suffering from multiple, recurrent BCCs. Patient characteristics are given in *Table I*. On examination patient 1 presented with 3 newly detected superficial BCC on her neck and face. Patient 2 showed 5 superficial BCC on her lower leg and trunk whereas patient 3 had 10 newly diagnosed, superficial lesions in multiple locations, mainly face and trunk. The size of the lesions ranged from 1-5 cm in diameter in all patients. No basal cell nevi were found in any of the patients at the time of their pre-treatment visit. Both daughters of patient 1 reported NBCCS lesions, however in the families of patients 2 and 3 no other cases of

Patient 1 suffered from breast cancer of the left mamma, which had been treated successfully by ablation in 1996. All patients were treated topically on BCC sites *(Fig. 1A)* with 5% imiquimod cream (Aldara(tm), 3M Health Care) 3 times per week for 6 to 8 weeks. Photographs were taken of lesions before treatment *(Fig. 1A)*, after 5 weeks *(Fig. 1B)* and 8 weeks *(Fig. 1C)* of treatment, and during a follow-up visit 2 weeks after treatment finished *(Fig. 1D)*. The only adverse events reported were erythema *(Fig. 1B, C)* and itching, and mild erosion — however these events were rated mild in all cases and no additional treatment was required. In the event of a local skin reaction, application of imiquimod was decreased from 3 to 2 times per week *(Fig. 1C)*. Clinical examination 2 weeks after treatment finished showed that all treated BCCs had been completely cleared *(Fig. 1D)*. All lesions were biopsied 1 week before before application of imiquimod *(Fig. 2A)* and 2 weeks after treatment was completed *(Fig. 2B)*. Tissues were stained with heamatoxylin and eosin. Photomicrographs of specimens taken from skin lesions *(Fig. 2A)* show the typical criteria for BCCs. Histologically no signs imiquimod therapy *(Fig. 2B)*. Patients showed no recurrence during a 12-month follow-up period.

Discussion

The Gorlin-Goltz syndrome, also known as naevoid basal cell carcinoma syndrome (NBCCS), represents an autosomal dominant disorder with a wide variety of primary symptoms. BCCs represent a major problem due to their early invasion of deep structures [1], particularly in sun exposed areas of the skin. NBCCS is caused by a genetic mutation in PTCH, a human homolog of the drosophila patched gene [10-13]. Mutations in PTCH and SMOH are responsible for the aetiology of BCCs in general [14, 15]. The current treatment of BCCs in Gorlin-Goltz syndrome is a multiple-modality treatment dominated by cryotherapy and extensive surgery [16] which is often painful. This mode of treatment does not affect the naturally high rate of formation of new BCC lesions in patients with this syndrome.

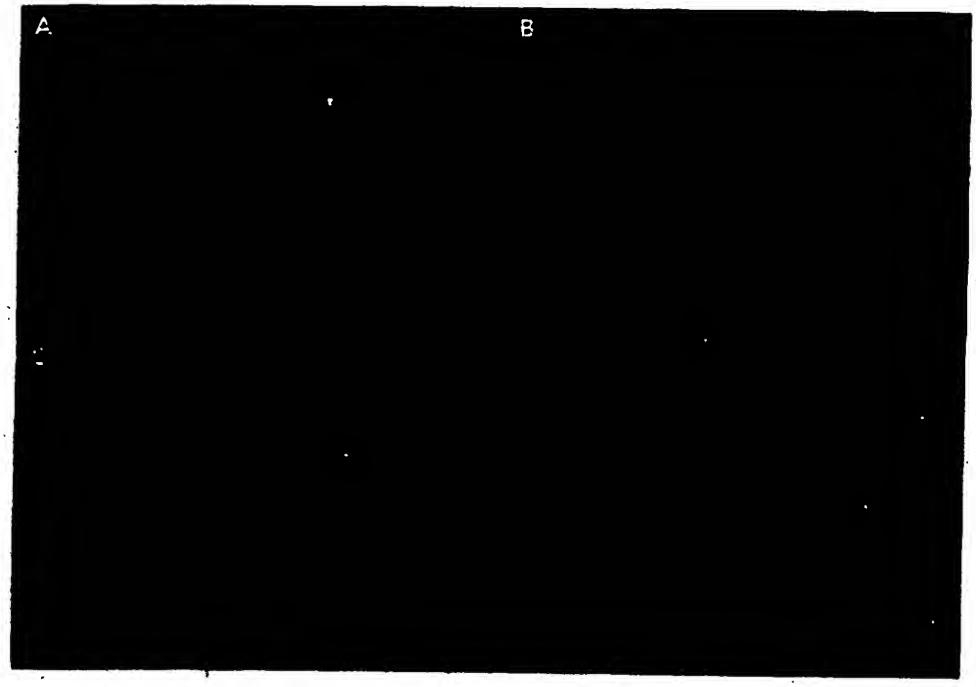

Figure 1. *A BCC lesion on the forehead of patient 1 before treatment (A), and after 5 (B) and 8 (C) weeks treatment with 5% imiquimod cream. Due to local skin reactions (erythema) imiquimod application was reduced from 3 to 2 times per week after 6 weeks. The lesion was diagnosed as clinically clear 2 weeks after treatment finished (D).*

Table I. *Characteristics of three Gorlin-Goltz syndroms-patients with multiple BCCs*

Patient	Sex Age	Number of BCCs previously treated	Previous Therapy	Newly diagnosed BCCs	Main BCC locations	Results of treatment
1	Female 78	> 200 BCCs	Excision, Jawcyst-ectomy, ablatio mammae	3 superficial BCCs	Face and neck	Total clearance of all BCCs in treated area
2	Female 61	> 300 BCCs	Excision, radiation (in 1975)	5 superficial BCCs	Left lower leg and trunk	Total clearance of all BCCs in treated area
3	Male 37	> 100 BCCs	Excision	10 superficial BCCs	Multiple locations	Total clearance of all BCCs in treated area

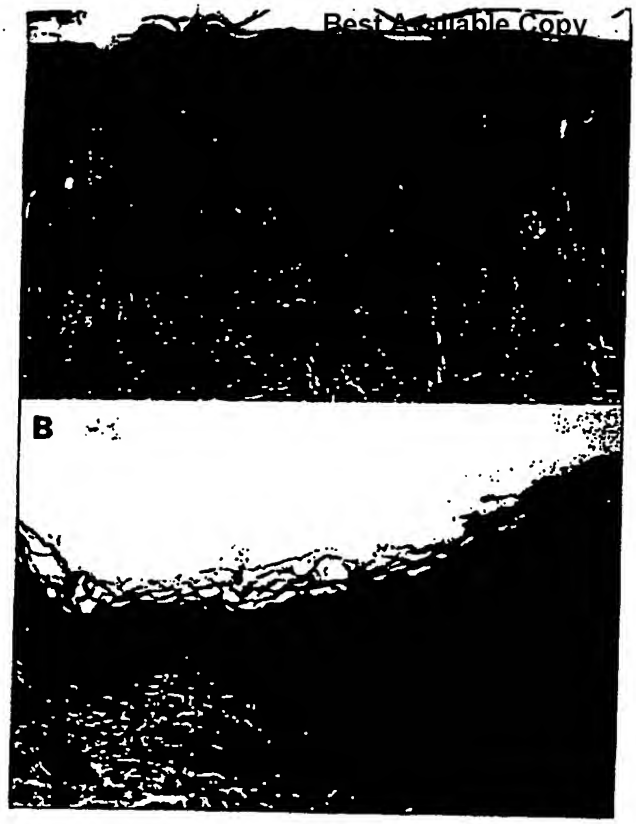

Figure 2. *Hematoxylin and eosin stained sections taken from the BCC lesion on patient 1* (Fig. 1). *Punch biopsies were taken one week before treatment was iniated (A) and 2 weeks after (B) treatment with 5% imiquimod cream finished. Treatment with imiquimod successfully resolved the lesion.*

The case studies reported here indicate that topical application of 5% imiquimod cream 2 to 3 times per week for 6 to 8 weeks is an effective regime for treatment of BCCs in patients with NBCCS. BCCs clearly regressed in all 3 patients, with no new or recurrent lesions observed during the 12-month follow-up period.

Imiquimod is currently used as an effective treatment for external genital warts [22], and has been used successfully in the treatment of BCCs in humans [21]. Results from previous studies investigating the mode of action of imiquimod suggest that regression of BCC lesions after imiquimod treatment may result from immune-mediated processes. Skin biopsies from hairless mice treated with 5% imiquimod showed upregulation Interferon-α (IFNα), IFNβ, tumor necrosis factor α (TNFα), IL-1α, IL-1β, IL-6, and IL-12 [23]. Therefore, imiquimod does not interact with tumour cells directly, but induces production of pro-inflammatory cytokines which up-regulate the body's own immune response to malignant cells.

A recent publication by Kagy and Amonette [24] also reported the successful treatment of BCCs in NBCCS with daily application of 5% imiquimod cream for 18 weeks. However, the patient suffered a strong local inflammatory response to treatment. Our results indicate that a reduction in the number of applications of imiquimod from 3 times red lesions in 8 weeks or less. This indicates that imiquimod may be an effective treatment for BCCs in NBCCS. However, further clinical trials are needed to assess the efficacy and tolerability of imiquimod for this disorder.

In all our patients, topical application of 5% imiquimod cream 2 to 3 times per week proved to be a successful treatment for BCCs, without any severe side effects. Imiquimod and other related immune response modifiers may therefore provide a novel approach in the non-surgical therapy of BCCs in Gorlin-Goltz syndrome. ■

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Figures 1 and 2. *Erythematous areas with many non itching, fine, keratotic papules of the cheeks, neck and shoulders.*

Ulerythema ophryogenes and keratosis pilaris

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This case was presented as a poster in the VIII EADV Congress Amsterdam, 29 September-3 October 1999.

A 17-year-old girl presented with poor growth and mental retardation with dysmorphic features including a round broad face with a high forehead, protruding ears, ptosis, epicanthal folds, hypertelorism, broad nasal bridge, downturning corners of the mouth and wide mouth with protruding upper lip; early dental caries and skeletal defects consisting of mild megalodyscrania, abnormal accentuation of left parietal bone, brachycephaly, micrognathia, cranial and carpal dysostosis.
Family history revealed that the parents were unrelated and healthy, although the mother was aged 40 and the father 50 when the child was born. Hepatomegaly and splenomegaly were present at birth, as well as an intraventricular wall defect. Because of hyposomia (growth measurements under third percentile) she had then been followed by our Department of Pediatrics. Karyotype analysis was performed at the age of 3 years and a chromosome 18p deletion was found. At the same age ophthalmologic examination revealed a mild defect of the inferior oblique muscle, resulting in an elevation deficit. Exophoria was also detected. Toward the 8th year of life the girl's developmental skills appeared behind those of her contemporaries. Dermatologic examination revealed 3 café-au-lait spots on the abdomen, low back hairline, erythematous areas with many non itching, fine, keratotic papules of the neck, shoulders, upper back and thighs as well as the eyebrows, chin and cheeks *(Figs. 1* and *2)*. Histologic examination revealed compact orthokeratotic hyperkeratosis of the follicular infundibulus and peri-infundibular fibrosis.
Most patients with 18p-syndrome have neither keratosis pilaris (KP) nor ulerythema ophryogenes (UO) but 3 cases of UO and KP associated with 18p monosomy have been recently reported in the literature [1-3]. UO and KP, also named KP atrophicans faciei, is one of the four clinical types of KP atrophicans which typically affects the eyebrows and cheeks, although forehead, ears and scalp can be involved. Non atrophicans KP may be associated. UO and KP may present an autosomal dominant pattern of inheritance and they are not infrequently associated with various genetic defects. Recently a defect in the laminin alpha1 chain (encoded by the LAMA1 gene localized at position 18p11.3) has been suggested to be involved in this disorder [4, 5], although further studies are necessary to confirm this hypothesis or to identify other genes associated with follicular morphogenesis located in the same 18p region.

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Therapeutics

Imiquimod 5% cream for the treatment of superficial and nodular basal cell carcinoma: randomized studies comparing low-frequency dosing with and without occlusion

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Summary

Background Imiquimod 5% cream has been investigated for non-surgical treatment of superficial and nodular basal cell carcinoma (BCC) tumours.

Objectives Two studies were conducted to examine the effect of occlusion at low dosing frequencies on the safety and efficacy of topical imiquimod 5% cream for the treatment of superficial and nodular BCC.

Patients and methods Both open-label studies were conducted in Europe. Patients diagnosed with BCC were enrolled into either the superficial (93 patients) or nodular (90 patients) study, depending on the histological confirmation of the patient's tumour subtype. Patients were randomized to one of four groups to apply imiquimod 5% cream 2 or 3 days per week either with or without occlusion. Six weeks following a 6-week treatment period, the entire target tumour area was excised and histologically examined for evidence of residual tumour.

Results In both studies, the highest histologically complete response rate was seen in the 3 days per week with occlusion groups, with complete response rates of 87% and 65% for the superficial and nodular studies, respectively. Occlusion did not have a statistically significant effect on response rate at either dosing frequency. Response rates for superficial and nodular BCC tumours treated 3 days per week without occlusion were 76% and 50%, respectively.

Conclusions In the superficial study, the complete response rate of 87% in the 3 days per week with occlusion group was similar to that of daily and 5 days per week dosing without occlusion in a previous 12-week study and one study of daily dosing without occlusion for 6 weeks. All treatment groups had acceptable safety profiles in both studies. Occlusion did not have a statistically significant effect on efficacy for either superficial or nodular BCC tumours.

Key words: basal cell carcinoma, imiquimod, nodular, superficial

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All enrolling investigators are listed in the Acknowledgments.

The immune response modifier, imiquimod, is sold as a 5% topical cream (Aldara®) for the treatment of genital warts. Preclinical studies have shown that imiquimod promotes antiviral[1] and antitumour[2] effects due to the induction of cytokines[3] such as interferons and others. Because of the antitumour activity associated with imiquimod, the 5% cream formulation is being studied as a potential alternative to surgical therapies for the treatment of basal cell carcinoma (BCC).

Pilot studies in patients with BCC have demonstrated that imiquimod 5% cream is efficacious in clearing these tumours.[4] Complete response rates for superficial BCC[5] following treatment with imiquimod 5% cream have been higher than those for nodular BCC.[6] The difference in treatment outcomes for superficial and nodular BCCs is speculated to be attributable to the biology of the tumour.

It has been previously published that the most effective dosing regimen for both superficial and nodular BCC is once daily 7 days per week for a period of at least 6 weeks.[5,6] The side-effects of using imiquimod cream are most often application site reactions. Higher topical dosing frequencies have demonstrated an increase in the frequency of application site reactions and the need for rest periods, while lower dosing frequencies have shown reduced efficacy rates.[4] An imiquimod pilot study (data on file at 3M) using occlusion to treat BCC showed twice daily 7 days per week dosing was not tolerated by subjects. In clinical practice, occlusion has an established role in increasing the observed activity of a variety of agents.[7,8] The two studies reported here sought to address the question of whether occlusion of the skin during treatment of superficial or nodular BCC with imiquimod 5% cream would lead to an enhanced efficacy profile at low dosing frequencies.

Patients and methods

These were multicentre, open-label, randomized studies performed in Europe. As both studies used similar protocols, the methods reported here will pertain to both unless otherwise stated.

Patients

Patients were eligible for these studies if they were at least 18 years old and had a primary tumour that was histologically confirmed to be superficial or nodular BCC. Target tumours were to be between 0·5 cm^2 and 2·0 cm^2 in area for the superficial BCC study and 0·25 cm^2 and 1·5 cm^2 in area for the nodular BCC study (the difference in tumour area criteria was due to enrolment issues). Target tumours could be located on the limbs (excluding hands and feet), trunk (excluding anogenital area), neck, or head (high-risk areas within 1 cm of hairline, eyes, nose, mouth, or ears excluded). The tumour location criteria were expanded in the nodular study to include tumours in high-risk locations of the scalp, nose, mouth, and ears.

Patients were excluded if they had any previous therapy to the target tumour or if they had any dermatological conditions that would interfere with local assessments.

Methods

Interventions

Two studies were conducted; one examined superficial BCC and another examined nodular BCC. Both studies consisted of a screening visit, a 6-week treatment period with regular interval visits, and a post-treatment visit 6 weeks following the end of treatment for surgical excision of the target tumour area. Patients were randomized to one of four dosing regimens: 2 days per week with or without occlusion, or 3 days per week with or without occlusion. Within each study, a computer-generated randomization schedule assigned patients in blocks of four to each dosing regimen. Study personnel were blinded to this randomization schedule until after subject treatment assignments had been made. At the screening visit, patients were informed of study procedures and of their rights and responsibilities as study participants. All patients signed an ethics committee-approved informed consent document. Patients then had a confirmatory biopsy of their target tumour. At the initiation visit (2 weeks to 1 month following screening), a baseline tumour area was determined by measuring and multiplying the two largest perpendicular dimensions of the tumour. The tumour site and appropriate anatomic landmarks were mapped using a clear plastic sheet as a template to guide the excision at the end of the study. Six weeks following the end of treatment, patients underwent surgical excision of their target tumour for histological evaluation of response.

Biopsies

Each patient underwent a prestudy confirmatory punch, deep shave, or wedge biopsy of the target

tumour. Investigators were encouraged to remove no more than approximately 25% of the tumour. Biopsies extended into the reticular dermis and all specimens were sent to an independent dermatopathology laboratory where they were sectioned and histologically examined for superficial or nodular BCC. Superficial BCC was defined as a multifocal tumour exhibiting atypical basaloid cells extending from the epidermis and the tumour was to be confined to the superficial portion of the papillary dermis. Nodular BCC was defined as a tumour showing nodular aggregates of atypical basaloid cells extending into the reticular dermis with peripheral, palisading, mitotic figures, and clefting from a surrounding fibromyxoid stroma. Patients diagnosed with superficial BCC with nodular components were enrolled into the nodular study.

Study cream application

Patients were instructed to gently clean and dry the target tumour area with soap and water and apply topical imiquimod cream just prior to their normal bedtime according to the dosing regimen to which they were assigned. Patients dispensed cream from single-use sachets and rubbed the cream into the tumour area using an estimated amount of study cream determined by the larger diameter of each patient's tumour. An area approximately 1 cm surrounding the tumour was covered and the cream was left in place for at least 8 h.

Patients randomized to a 2 days per week schedule were asked to apply cream on the same 2 days every week, the first application being followed by 2 days without treatment, and the second application being followed by 3 days without treatment (e.g. Monday and Thursday). Patients on a 3 days per week regimen were asked to apply study cream every other day, the last application of the week being followed by 2 days with no treatment (e.g. Monday, Wednesday, Friday). Patients randomized to either of the occlusion treatment groups covered their treatment site with 3M Clean Seals® Transparent Dressing while the cream was on the skin. Investigators could prescribe rest periods from treatment if the patient was unable to apply doses due to local skin reactions or treatment site adverse events.

End-of-treatment excision

Six weeks following the end of treatment, each patient underwent surgical excision of the target tumour area. Tumours were surgically excised with a 3–4 mm margin surrounding the tumour. Each excision specimen was cut into slices of no more than 3 mm thick that were then paraffin-processed, stained with haematoxylin and eosin and histologically examined for residual BCC using light microscopy. All sections were examined by two dermatopathologists for residual BCC and to ensure that the margins were free of tumour.

Safety and efficacy measurements

Patients returned to the study centre at the end of treatment weeks 1, 2, 4 and 6, and 6 weeks post-treatment for safety and efficacy evaluations. Prestudy and post-study evaluations included physical examinations, haematology, blood chemistry, urinalysis, and pregnancy tests for women of childbearing potential. Target tumours were measured and photographed prior to the prestudy biopsy, at treatment initiation, at each interval visit, and at the 6-week post-treatment visit prior to the excision. The presence and intensity of specific local skin reactions that have been seen in previous imiquimod studies (i.e. erythema, oedema, induration, vesicles, erosion, ulceration, excoriation/flaking and scabbing) were assessed by the investigator at interval visits and at the post-treatment excision visit and rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Vital signs measurements were taken at prestudy, initiation, and all interval visits. Concomitant medications and adverse events were monitored at interval visits and the post-treatment excision visit. At the post-treatment excision visit, investigators made clinical assessments of patients' tumour sites to determine whether BCC was evident. Excision specimens were examined histologically for evidence of remaining BCC.

Analyses

Sample size calculations were based on the ability to detect differences in complete response rates. Eighteen patients in each of the imiquimod dose groups gave these studies at least 80% power to detect a difference of 20% for one imiquimod dose group vs. 80% for another imiquimod dose group, assuming that each comparison was carried out at an alpha level of 0·05/4. The statistical analysis was performed on the intent-to-treat data set, which included all randomized patients. The primary variable was the complete response rate, defined as the proportion of patients who had no histological evidence of BCC in the 6-week post-treatment excision specimen. Patients who did not return for the post-treatment excision were considered

Table 1. Patient demographics (superficial study)

	2 days per week w/o occlusion ($n = 24$)	2 days per week with occlusion ($n = 21$)	3 days per week w/o occlusion ($n = 25$)	3 days per week with occlusion ($n = 23$)	Overall ($n = 93$)
Sex					
Male	16 (67%)	14 (67%)	14 (56%)	15 (65%)	59 (63%)
Female	8 (33%)	7 (33%)	11 (44%)	8 (35%)	34 (37%)
Age in years (mean ± SD)	69 ± 8·5	63 ± 14·2	61 ± 13·9	58 ± 15·8	63 ± 13·8
Median target tumour size (cm^2)	1·0	1·5	1·0	1·2	1·0
Target tumour location					
Face: forehead	2 (8·3%)	0 (0·0%)	0 (0·0%)	0 (0·0%)	2 (2·2%)
Neck	1 (4·2%)	1 (4·8%)	0 (0·0%)	0 (0·0%)	2 (2·2%)
Trunk	14 (58·3%)	14 (66·7%)	16 (64·0%)	16 (69·6%)	60 (64·5%)
Upper extremity (not hand)	5 (20·8%)	4 (19·0%)	7 (28·0%)	5 (21·7%)	21 (22·6%)
Lower extremity (not foot)	2 (8·3%)	2 (9·5%)	1 (4·0%)	2 (8·7%)	7 (7·5%)
Mons pubis	0 (0·0%)	0 (0·0%)	1 (4·0%)	0 (0·0%)	1 (1·1%)

non-responders for analysis purposes. Investigator assessments of whether or not the target tumours were clinically evident at the post-treatment excision visit were compared to histology results and positive and negative predictive values were calculated.

Fisher's exact test was used to compare the complete response rates among all four treatment groups for each study. If this overall test was significant, Fisher's exact tests were then used to compare complete response rates in the following pairwise comparisons: 2 days per week with occlusion vs. 2 days per week without occlusion; 3 days per week with occlusion vs. 3 days per week without occlusion; 2 days per week with occlusion vs. 3 days per week with occlusion; and 2 days per week without occlusion vs. 3 days per week without occlusion. Each comparison was carried out at an alpha level of 0·05/4 in order to preserve the overall alpha level of 0·05.

Results: Superficial basal cell carcinoma study

Ninety-three patients (59 males and 34 females) were enrolled (Table 1). Target tumours ranged in size from 0·2 to 3·8 cm^2 and were most frequently located on the trunk. Fifteen patients had target tumours outside of the range (three smaller, 12 larger) specified in the inclusion criteria but were allowed to continue in the study. Eight patients discontinued from the study (five due to personal reasons, one lost to follow-up, one due to an adverse event, and one due to a local skin reaction, Fig. 1).

Efficacy

Of the 93 patients, 88 underwent post-treatment excision (Figs 4,5). Five patients did not return for post-treatment excision and were considered treatment

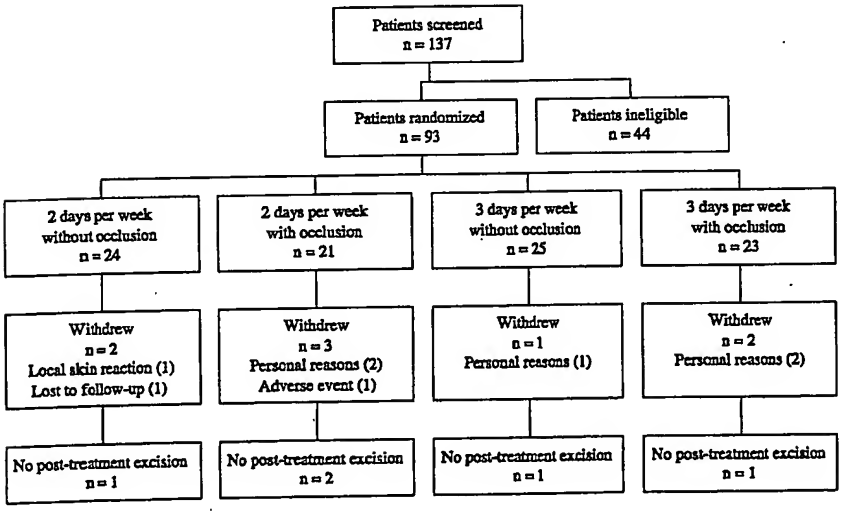

Figure 1. Superficial disposition.

failures in the analysis. The highest complete response rates (Fig. 2) were seen in the 3 days per week treatment groups with rates of 87% (20 of 23) and 76% (19 of 25) for patients with and without occlusion, respectively. Complete response rates for the 2 days per week treatment groups were 43% (nine of 21) and 50% (12 of 24) for patients with and without occlusion, respectively. Occlusion did not have a statistically significant effect on complete response rate at either dosing frequency. The complete response rate increased as dosing frequency increased, both with and without occlusion. However, the only statistically significant difference in response rate was seen when comparing the 2 days per week with occlusion and 3 days per week with occlusion groups ($P = 0{\cdot}004$).

The post-treatment investigator clinical assessment of target tumour clearance for 66 of 93 patients was compared to the histology result from the excision (Table 2). The overall negative predictive value for tumour assessment was 79·4%, which meant that 27 of 34 patients who were clinically assessed as negative (no tumour visually evident) were histologically confirmed to be negative for BCC. The overall positive predictive value was 46·9%, which indicated that 15 of 32 of patients who were clinically assessed as positive (tumour visually evident) were confirmed to be positive for BCC histologically. Twenty-two additional patients were assessed as 'unable to determine' and five patients did not have an assessment.

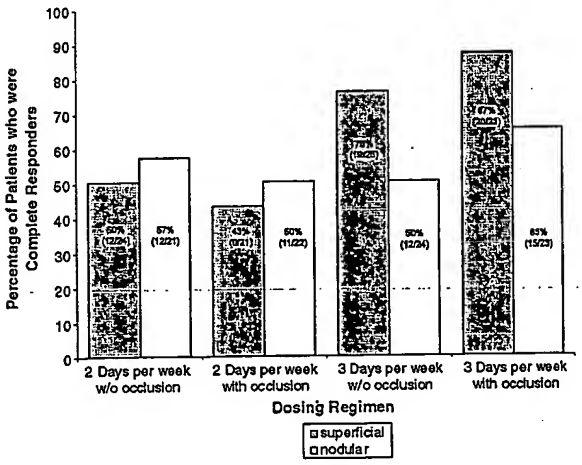

Figure 2. Complete response rates by dosing regimen.

Table 2. Post-treatment investigator assessment of clearance vs. histological result (superficial basal cell carcinoma, BCC)*

Investigator clinical assessment	Histological result		
	No BCC present	BCC present	Total
No BCC present	27*	7	34
BCC present	17	15	32
Total	44	22	66

*Number of patients.

Safety

Adverse events. Adverse events occurred in all treatment groups with 55 of 93 (59%) patients reporting at least one adverse event. Application site reactions, reported by 30 (32%) patients, were the most frequently reported adverse events. Itching, burning, and hypopigmentation at the target tumour site were the most commonly reported application site reactions. Two patients experienced severe application site reactions that were considered probably related to study drug. One patient (3 days per week with occlusion group) had severe burning at the application site but continued dosing with imiquimod without additional therapy. The other patient (2 days per week without occlusion group) had severe pus and inflammation at the target site. This patient interrupted dosing for 2 weeks and applied mupirocin (topical antibiotic) to the target tumour area. Both patients recovered from their severe adverse events and completed the study. The incidence of fever or influenza-like symptoms in any treatment group was low.

Four patients experienced serious adverse events: one patient was hospitalized with dystonia and diagnosed with mechanical cervicalgia (musculoskeletal neck pain), and three patients were hospitalized for excision of non-target BCCs, actinic keratoses, and/or naevi. None of these patients discontinued from the study and all recovered from their adverse events. Of the two patients who discontinued the study, one discontinued due to moderate erosion at the tumour site. The second patient discontinued due to neurological dysregulation, although this was not considered by the investigator to be related to imiquimod cream use. Rest periods were taken by two patients, one each from the 3 days per week with occlusion and 2 days per week without occlusion groups.

Local skin reactions. Local skin reactions occurred in all treatment groups. Most of the investigator assessments of these local skin reactions were mild to moderate in intensity, with erythema and induration occurring most frequently. Severe local skin reactions were reported in all treatment groups, although more frequently in the 3 days per week treatment groups than in the 2 days per week treatment groups. For

treatment 3 days per week, severe local skin reactions were more frequently reported in the occlusion group than in the non-occlusion group. This was opposite to the effect seen with 2 days per week dosing. Of the severe reactions, erythema occurred most often, followed by erosion.

Results: Nodular basal cell carcinoma study

Ninety patients (56 males and 34 females) were enrolled (Table 3). Target tumours ranged in size from 0·2 to 2·4 cm^2 and were most frequently located on the head followed by the trunk. Eight patients had target tumours outside of the range (four smaller, four larger) specified in the inclusion criteria but were allowed to continue in the study. Seven patients discontinued from the study (three due to adverse events, two due to local skin reactions, one lost to follow-up, and one due to expiration of the drug supply before the patient completed dosing, Fig. 3).

Efficacy

Eighty-nine of the 90 patients underwent post-treatment excision and 50 (55·6%) were complete responders to therapy with imiquimod (Figs 6,7). One patient did not return for the post-treatment excision and was considered a non-responder for analysis purposes. Complete response rates (Fig. 2) in the 3 days per week treatment groups of 65% (15 of 23) and 50% (12 of 24) were seen for patients with and without occlusion, respectively. Complete response rates for the 2 days per week treatment groups were 50% (11 of 22) and 57% (12 of 21) for patients with and without occlusion, respectively. No significant differences of complete response rate were detected between the four treatment groups ($P = 0·700$).

Table 3. Patient demographics (nodular study)

	2 days per week w/o occlusion ($n = 21$)	2 days per week with occlusion ($n = 22$)	3 days per week w/o occlusion ($n = 24$)	3 days per week with occlusion ($n = 23$)	Overall ($n = 90$)
Sex					
Male	16 (76%)	11 (50%)	13 (54%)	16 (70%)	56 (62%)
Female	5 (24%)	11 (50%)	11 (46%)	7 (30%)	34 (38%)
Age in years (mean ± SD)	67 ± 8·9	66 ± 13·2	66 ± 13·2	66 ± 14·6	66 ± 12·5
Median target tumour size (cm^2)	1·0	0·6	0·6	0·7	0·7
Target tumour location					
Scalp	0 (0%)	1 (4·5%)	0 (0%)	0 (0%)	1 (1·1%)
Face	9 (42·9%)	10 (45·5%)	11 (45·8%)	18 (78·3%)	48 (53·3%)
Neck	3 (14·3%)	5 (22·7%)	2 (8·3%)	1 (4·3%)	11 (12·2%)
Trunk	7 (33·3%)	4 (18·2%)	6 (25·0%)	2 (8·7%)	19 (21·1%)
Upper extremity (not hand)	1 (4·8%)	2 (9·1%)	4 (16·7%)	2 (8·7%)	9 (10·0%)
Lower extremity (not foot)	1 (4·8%)	0 (0·0%)	1 (4·2%)	0 (0·0%)	2 (2·2%)

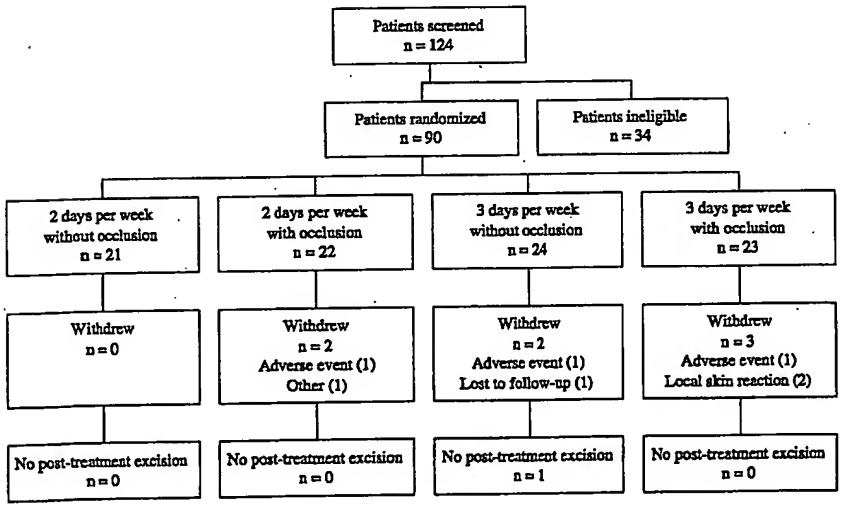

Figure 3. Nodular disposition.

Table 4. Post-treatment investigator assessment of clearance vs. histological result (nodular basal cell carcinoma, BCC)*

Investigator clinical assessment	Histological result		
	No BCC present	BCC present	Total
No BCC present	17*	4	21
BCC present	15	33	48
Total	32	37	69

*Number of patients.

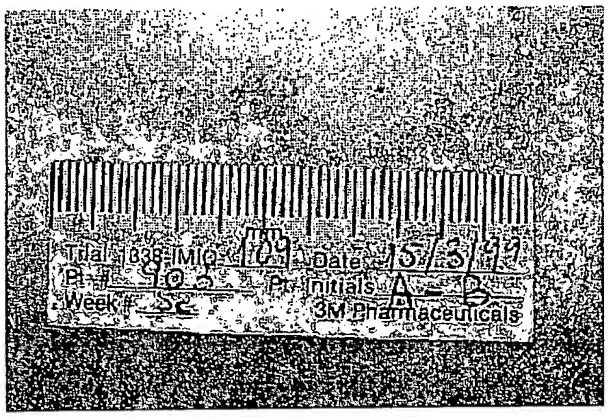

Figure 4. Superficial basal cell carcinoma (target tumour) prior to treatment.

Post-treatment clinical assessment data for 69 of 90 patients' target tumours were compared to histology results from excisional biopsies (Table 4). Twenty additional patients were assessed as 'unable to determine' and one additional patient did not have an assessment. The overall negative predictive value for tumour assessment was 81·0%, which meant that 17 of 21 treated tumours that were clinically assessed as negative (no tumour present) were histologically confirmed to be negative for BCC. The overall positive predictive value was 68·8%, which indicated that 33 of 48 treated tumours that were assessed as positive (tumour clinically evident) were confirmed to be positive for BCC histologically.

Safety

Adverse events. A total of 63 (70%) patients reported at least one adverse event during the study. Application site reactions, reported by 38 (42%) patients, were the most frequently reported adverse events. Of application site reactions, itching, irritation, and bleeding were the most frequently reported. Five patients experienced severe application site reactions that were considered probably related to the study drug. In the 3 days per week with occlusion group, one patient reported continuous stinging and pain at the application site. Another patient reported irritation at the target tumour and one patient reported irritation and pruritus. In the 3 days per week without occlusion group, one patient experienced local irritation and one patient in the 2 days per week with occlusion group experienced persistent inflammation. Two of the five patients

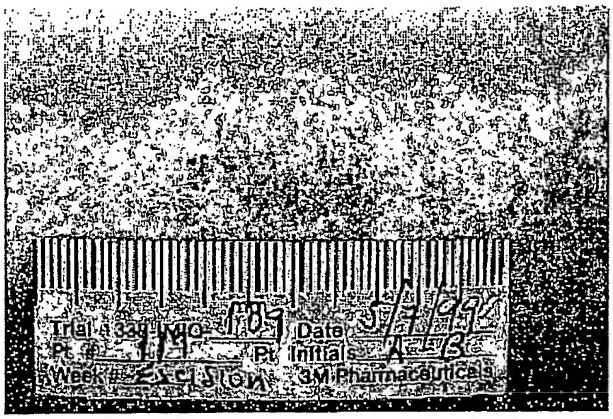

Figure 5. Post-treatment, prior to excision (clinically and histologically clear).

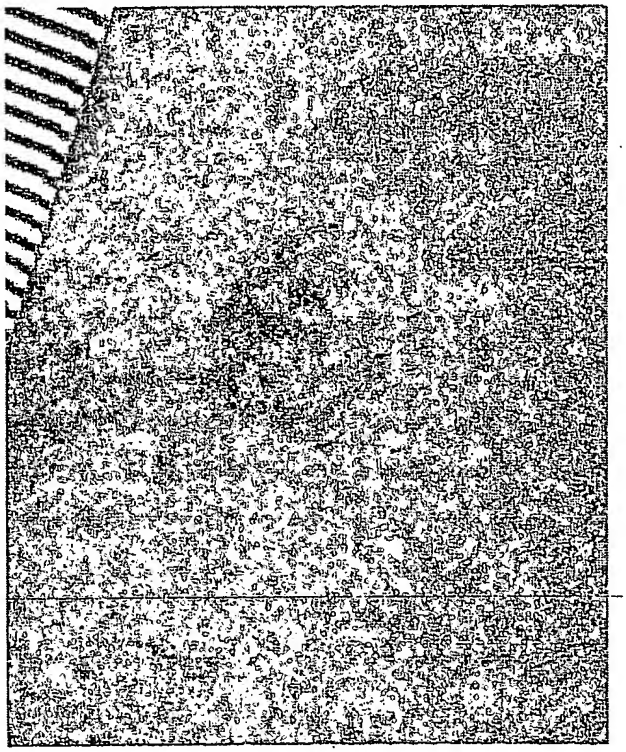

Figure 6. Nodular basal cell carcinoma (target tumour) prior to treatment.

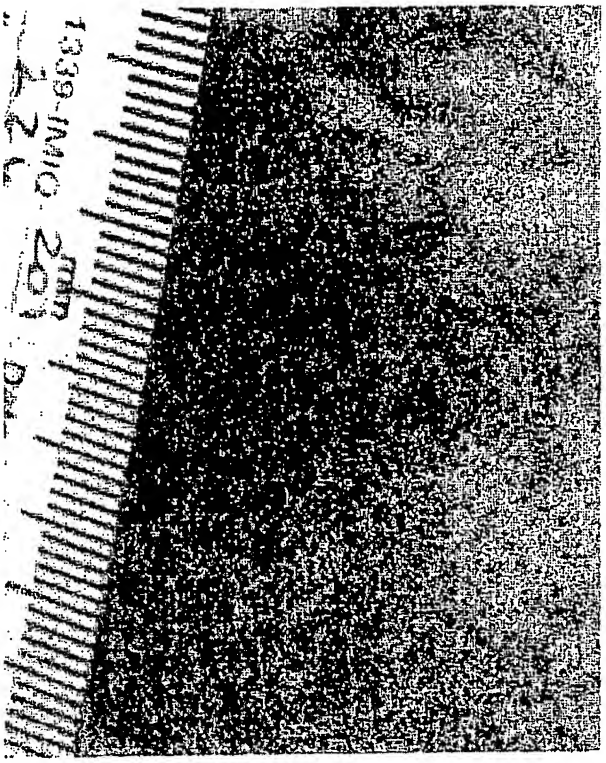

Figure 7. Post-treatment, prior to excision (clinically and histologically clear).

interrupted imiquimod treatment and three stopped treatment; none of these patients required additional therapy.

Four patients experienced serious adverse events. Although none of these events were considered to be related to the study drug, they included one patient who was hospitalized with coxarthrosis of the hip, one patient hospitalized for knee surgery, one patient hospitalized for fracture of the radius and one patient hospitalized for excisional surgery of a non-target BCC on the nose and sebaceous gland hyperplasia on the forehead. None of these patients discontinued from the study. Of the five patients who discontinued treatment due to adverse events, two discontinued because of local skin reactions (one due to severe erythema and oedema and one due to erythema, oedema and crust) and three discontinued because of application site reactions (one due to inflammation at the target site and two due to irritation at the target site). All patients recovered from their adverse events.

Local skin reactions. Local skin reactions occurred in all treatment groups, with erythema being the most frequently reported. In the 3 days per week with occlusion group, 10 of 23 (43%) patients reported severe erythema. Severe local skin reactions were reported in all treatment groups, although more frequently in the 3 days per week treatment groups than in the 2 days per week treatment groups, and more frequently in the occlusion groups than in the non-occlusion groups. The incidence of severe erythema decreased as the frequency of dosing decreased and the incidence of severe erythema was higher in the groups that used occlusion than in the groups without occlusion. Rest periods were taken by three patients (two in the 3 days per week with occlusion group and one in the 3 days per week without occlusion group).

Discussion

In a pilot study using imiquimod to treat BCC tumours with occlusion, it was found that twice-daily dosing was not tolerated. In an effort to examine the safety and efficacy effects of occlusion using lower frequency dosing, these two studies were initiated. In these studies, occlusion did not have a statistically significant effect on efficacy within either dosing frequency for either superficial or nodular BCC. Although the differences in response rates between the occlusion and non-occlusion groups were not found to be statistically significant, these studies were designed to detect large differences.

Clearance rates for superficial BCC at 3 days per week dosing were statistically significantly greater than the rate for twice-weekly dosing. The efficacy rates in the superficial study for 3 times per week dosing with occlusion are similar to efficacy rates of 5 days per week and daily dosing without occlusion seen in a previous 12-week study[9] and daily dosing without occlusion in a 6-week study.[5] Available supportive evidence from previous studies indicates that a minimum threshold for effective dosing for superficial BCC may be 3 days per week. The efficacy rates in the 2 days per week dosing regimen are inadequate to recommend imiquimod 5% cream for the treatment of either superficial or nodular BCC at that dosing frequency. Even with occlusion at 3 days per week, nodular BCC remains less responsive to imiquimod than superficial BCC. This is consistent with previously published studies. Although BCC is rarely fatal, its morbidity rate is high and BCC often causes discomfort and distress to the patient, as well as an extra cost burden to the health industry. Currently, of the 6-week studies treating superficial and nodular BCC with

imiquimod, the most effective dosing regimen remains once daily 7 days per week.[5,6]

When balancing the risk–benefit ratio, it is evident from these results that the decreased frequency of imiquimod application does increase the tolerability to the patient, which may positively influence compliance. The safety profiles seen here were milder than those seen with more frequent dosing regimens of imiquimod as evidenced by the low rate of severe local skin reactions as well as the infrequent need for rest periods.

The small effect of occlusion on complete response rate in these studies may be due to several factors. One factor may be suboptimal drug penetration into the tumour. The water solubility of imiquimod is low and this may partially account for the failure of occlusion and any increased state of hydration of the epidermis to enhance the activity of imiquimod. However, as the local skin reactions seen in these studies were consistent with the induction of a local inflammatory response at the target tumour, this is likely a sign of sufficient penetration. An alternative possibility may reflect biological aspects of the immune response itself. It may be that the pathways involved are already near maximum stimulation, allowing no additional benefit from occlusion.

A factor for the different response rate between superficial and nodular BCC may be the migration of educated T cells and release of cytokines into surrounding areas of the tumour. As superficial BCCs are thin and flat, they provide more surface area in contact with immune cells and cytokines than the more spherical, compact, nodular tumour, thus increasing the likelihood of tumour clearance.

The pre-excision negative predictive values for both studies were higher than the positive predictive values, indicating that investigators accurately assessed the absence of a tumour more often than they accurately assessed the presence of one. In view of the reaction elicited by imiquimod treatment, evidence is accumulating that the time interval of 6 weeks post-treatment may not be long enough to allow the visible signs of this reaction to abate. In clinical practice, where physicians are not bound to the requirements of a study protocol, the clinician will have the option of reviewing the patient at a time of their choosing after a few months (a timeframe similar to that used when assessing patients who have undergone surgical treatment). The evidence of persistent tumour will most likely become increasingly obvious with time while the appearance of a resolving or cleared tumour would tend to improve.

Acknowledgments

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ALDARA™

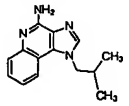
[al dar' a]
(imiquimod)
Cream, 5%

For Dermatologic Use Only –
Not for Ophthalmic Use.

DESCRIPTION

Aldara™ is the brand name for imiquimod which is an immune response modifier. Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.

Chemically, imiquimod is 1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-4-amine. Imiquimod has a molecular formula of $C_{14}H_{16}N_4$ and a molecular weight of 240.3. Its structural formula is:



CLINICAL PHARMACOLOGY

Pharmacodynamics

Imiquimod has no direct antiviral activity in cell culture. A study in 22 patients with genital/perianal warts comparing imiquimod and vehicle shows that imiquimod induces mRNA encoding cytokines including interferon-α at the treatment site. In addition HPVL1 mRNA and HPV DNA are significantly decreased following treatment. However, the clinical relevance of these findings is unknown.

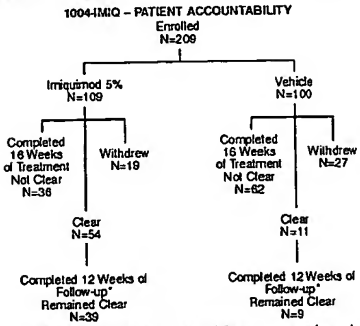
Pharmacokinetics

Percutaneous absorption of [^{14}C] imiquimod was minimal in a study involving 6 healthy subjects treated with a single topical application (5 mg) of [^{14}C] imiquimod cream formulation. No radioactivity was detected in the serum (lower limit of quantitation: 1 ng/mL) and <0.9% of the radiolabeled dose was excreted in the urine and feces following topical application.

CLINICAL STUDIES

In a double-blind, placebo-controlled clinical trial, 209 otherwise healthy patients 18 years of age and older with genital/perianal warts were treated with Aldara 5% cream or vehicle control 3X/week for a maximum of 16 weeks. The median baseline wart area was 69 mm² (range 8 to 5525 mm²). Patient accountability is shown in the figure below.

1004-IMIQ – PATIENT ACCOUNTABILITY



*The other patients were either lost to follow-up or experienced recurrences.

Data on complete clearance are listed in the table below. The median time to complete wart clearance was 10 weeks.

CLEARANCE – STUDY 1004

Treatment	Patients With Complete Clearance of Warts	Patients Without Follow-up	Patients With Warts Remaining at Week 16
Overall			
imiquimod 5% (N=109)	50%	17%	33%
vehicle (N=100)	11%	27%	62%
Females			
imiquimod 5% (N=46)	72%	11%	17%
vehicle (N=40)	20%	33%	48%
Mates			
imiquimod 5% (N=63)	33%	22%	44%
vehicle (N=60)	5%	23%	72%

INDICATIONS AND USAGE

Aldara 5% cream is indicated for the treatment of external genital and perianal warts/condyloma acuminata in individuals 12 years old and above.

CONTRAINDICATIONS

None known

WARNINGS

Aldara cream has not been evaluated for the treatment of urethral, intra-vaginal, cervical, rectal, or intra-anal human papilloma viral disease and is not recommended for these conditions.

PRECAUTIONS

General

Local skin reactions such as erythema, erosion, excoriation/flaking, and edema are common. Should severe local skin reaction occur, the cream should be removed by washing the treatment area with mild soap and water. Treatment with Aldara cream can be resumed after the skin reaction has subsided. There is no clinical experience with Aldara cream therapy immediately following the treatment of genital/perianal warts with other cutaneously applied drugs; therefore, Aldara cream administration is not recommended until genital/perianal tissue is healed from any previous drug or surgical treatment. Aldara has the potential to exacerbate inflammatory conditions of the skin.

Information for Patients

Patients using Aldara 5% cream should receive the following information and instructions: The effect of Aldara 5% cream on the transmission of genital/perianal warts is unknown. Aldara 5% cream may weaken condoms and vaginal diaphragms. Therefore, concurrent use is not recommended.

GLUED PANEL
(Does not print)

1. This medication is to be used as directed by a physician. It is for external use only. Eye contact should be avoided.
2. The treatment area should not be bandaged or otherwise covered or wrapped as to be occlusive.
3. Sexual (genital, anal, oral) contact should be avoided while the cream is on the skin.
4. It is recommended that 6-10 hours following Aldara 5% cream application the treatment area be washed with mild soap and water.
5. It is common for patients to experience local skin reactions such as erythema, erosion, excoriation/flaking, and edema at the site of application or surrounding areas. Most skin reactions are mild to moderate. Severe skin reactions can occur and should be reported promptly to the prescribing physician.

6. Application of Aldara cream in the vagina is considered internal and should be avoided. Female patients should take special care if applying the cream at the opening of the vagina because local skin reactions on the delicate moist surfaces can result in pain or swelling, and may cause difficulty in passing urine.

7. Some reports have been received of localized hypopigmentation and hyperpigmentation following Aldara use. Follow-up information suggests that these skin color changes may be permanent in some patients.

8. Uncircumcised males treating warts under the foreskin should retract the foreskin and clean the area daily.

9. Patients should be aware that new warts may develop during therapy, as Aldara is not a cure.

Carcinogenicity, Mutagenesis, and Impairment of Fertility

Rodent carcinogenicity data are not available. Imiquimod was without effect in a series of eight different mutagenicity assays including Ames, mouse lymphoma, CHO chromosome aberration, human lymphocyte chromosome aberration, SHE cell transformation, rat and hamster bone marrow cytogenetics, and mouse dominant lethal test. Daily oral administration of imiquimod to rats, at doses up to 8 times the recommended human dose on a mg/m^2 basis throughout mating, gestation, parturition and lactation, demonstrated no impairment of reproduction.

Pregnancy

Pregnancy Category B: There are no adequate and well-controlled studies in pregnant women. Imiquimod was not found to be teratogenic in rat or rabbit teratology studies. In rats at a high maternally toxic dose (28 times human dose on a mg/m^2 basis), reduced pup weights and delayed ossification were observed. In developmental studies with offspring of pregnant rats treated with imiquimod (8 times human dose), no adverse effects were demonstrated.

Nursing Mothers

It is not known whether topically applied imiquimod is excreted in breast milk.

Pediatric Use

Safety and efficacy in patients below the age of 12 years have not been established.

ADVERSE REACTIONS

In controlled clinical trials, the most frequently reported adverse reactions were those of local skin and application site reactions; some patients also reported systemic reactions. These reactions were usually mild to moderate in intensity; however, severe reactions were reported with 3X/week application. These reactions were more frequent and more intense with daily application than with 3X/week application. Overall, in the 3X/week application clinical studies, 1.2% (4/327) of the patients discontinued due to local skin/application site reactions. The incidence and severity of local skin reactions during controlled clinical trials are shown in the following table.

3X/WEEK APPLICATION
Wart Site Reaction as Assessed by Investigator

	Mild/Moderate				Severe			
	Females		Males		Females		Males	
	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157	5% Imiquimod N=114	Vehicle N=99	5% Imiquimod N=156	Vehicle N=157
Erythema	61%	21%	54%	22%	4%	0%	4%	0%
Erosion	30%	6%	29%	6%	1%	0%	1%	0%
Excoriation/ Flaking	18%	8%	25%	8%	0%	0%	1%	0%
Edema	17%	5%	12%	1%	1%	0%	0%	0%
Induration	5%	2%	7%	2%	0%	0%	0%	0%
Ulceration	5%	1%	4%	1%	3%	0%	0%	0%
Scabbing	4%	0%	13%	3%	0%	0%	0%	0%
Vesicles	3%	0%	2%	0%	0%	0%	0%	0%

Remote site skin reactions were also reported in female and male patients treated 3X/week with imiquimod 5% cream. The severe remote site skin reactions reported for females were erythema (3%), ulceration (2%), and edema (1%); and for males, erosion (2%), and erythema, edema, induration, and excoriation/ flaking (each 1%).

Adverse events judged to be probably or possibly related to Aldara reported by more than 5% of patients are listed below; also included are soreness, influenza-like symptoms and myalgia.

3X/WEEK APPLICATION

	Females		Males	
	5% Imiquimod N=117	Vehicle N=103	5% Imiquimod N=156	Vehicle N=158
Application Site Disorders:				
Application Site Reactions				
Wart Site:				
Itching	32%	20%	22%	10%
Burning	26%	12%	9%	5%
Pain	8%	2%	2%	1%
Soreness	3%	0%	0%	1%
Fungal Infection*	11%	3%	2%	1%
Systemic Reactions:				
Headache	4%	3%	5%	2%
Influenza-like symptoms	3%	2%	1%	0%
Myalgia	1%	0%	1%	1%

*Incidences reported without regard to causality with Aldara.

Adverse events judged to be possibly or probably related to Aldara and reported by more than 1% of patients include: Application Site Disorders: Wart Site Reactions (burning, hypopigmentation, irritation, itching, pain, rash, sensitivity, soreness, stinging, tenderness); Remote Site Reactions (bleeding, burning, itching, pain, tenderness, tinea cruris); Body as a Whole: fatigue, fever, influenza-like symptoms; Central and Peripheral Nervous System Disorders: headache; Gastro-Intestinal System Disorders: diarrhea; Musculo-Skeletal System Disorders: myalgia.

OVERDOSAGE

Overdosage of Aldara 5% cream in humans is unlikely due to minimal percutaneous absorption. Animal studies reveal a rabbit dermal lethal imiquimod dose of greater than 1600 mg/m^2. Persistent topical overdosing of Aldara 5% cream could result in severe local skin reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg was hypotension which resolved following oral or intravenous fluid administration.

DOSAGE AND ADMINISTRATION

Aldara cream is to be applied 3 times per week, prior to normal sleeping hours, and left on the skin for 6-10 hours. Following the treatment period cream should be removed by washing the treatad area with mild soap and water. Examples of 3 times per week application schedules are: Monday, Wednesday, Friday; or Tuesday, Thursday, Saturday application prior to sleeping hours. Aldara treatment should continue until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks. Local skin reactions (erythema) at the treatment site are common. A rest period of several days may be taken if required by the patient's discomfort or severity of the local skin reaction. Treatment may resume once the reaction subsides. Non-occlusive dressings such as cotton gauze or cotton underwear may be used in the management of skin reactions. The technique for proper dose administration should be demonstrated by the prescriber to maximize the benefit of Aldara therapy. Handwashing before and after cream application is recommended. Aldara 5% cream is packaged in single-use packets which contain sufficient cream to cover a wart area of up to 20 cm2; use of excessive amounts of cream should be avoided. Patients should be instructed to apply Aldara cream to external genital/perianal warts. A thin layer is applied to the wart area and rubbed in until the cream is no longer visible. The application site is not to be occluded.

HOW SUPPLIED

Aldara (imiquimod) cream, 5%, is supplied in single-use packets which contain 250 mg of the cream. Available as: box of 12 packets NDC 0089-0610-12.

Store below 25°C (77°F). Avoid freezing.

Keep out of reach of children.

Rx only

Manufactured by
3M Health Care Limited
Loughborough LE11 1EP England

Distributed by
3M Pharmaceuticals
Northridge, CA 91324

February 2003
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University of Miami Cosmetic Center*

is announcing a clinical research study to test a treatment for skin that has been aged and damaged by the sun (photoaging).

We are seeking female and male volunteers, 18 to 70 years of age with photoaging on the face. The treatment consists of a cream applied once daily to the face.

For more information call
Laura or Lucy at 305-324-SKIN (7546)

* The University of Miami Cosmetic Center
is physically located at Cedars Medical Center
1295 NW 14th Street, Suite K
Miami, FL 33125

EXHIBIT G

MEMORANDUM

DATE: May 12, 2003

TO: Dr. Leslie Bauman

FROM: Dr. Gary S. Margules for Patent and Copyright Committee

SUBJECT: Use of Aldara for the Treatment of Photoaged Skin (UM03-06)

We have assessed the Invention Disclosure with regards to commercial potential and have presented the Invention Disclosure to the Patent and Copyright Committee.

After careful review, the University of Miami wishes not to retain title to this invention, but instead wishes to release it to you, the inventor.

The condition of this release is:

- The University receives one sixth (1/6) of all gross proceeds, royalties, or other compensation received in exchange for an interest in or a right to use, sell, manufacture, distribute, or license such patent or invention by the inventor and any licensee, grantee, or assignee of the inventor, if such licensee, grantee, or assignee is related to the inventor, or if the inventor has a financial interest in such licensee, grantee, or assignee.

Each year the University receives numerous Invention Disclosures that cannot be accepted for commercialization for a wide variety of reasons. Our decision does not reflect unfavorably on your invention's scientific value but reflects more on commercial and business related factors.

Your submitting an Invention Disclosure is greatly appreciated and we encourage you to bring us other new inventions and discoveries in the future.

c: Dr. Norman Altman
Dr. Elizabeth Fenjves
File UM03-06